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Acid-Catalyzed Reaction of 2-Hydroxycyclobutanone with Benzylic Alcohols

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The acid-promoted syntheses of 2-(benzyloxy)cyclobutanones and bis(benzyloxy)dioxatricyclo decanes were achieved starting from 2-hydroxycyclobutanone and variously functionalized benzyl alcohols. The reaction sequences afforded the desired products in good to high yields and in a solvent-dependent chemoselective fashion.

Introduction

2-Hydroxycyclobutanones are useful intermediates in organic synthesis because of their rich chemical reactivity and inherent ring strain, and serve as well-defined molecular scaffolds thanks to their skeletal rigidity.[1] Such compounds have been used for the synthesis of a large variety of chemically and biologically interesting molecules.[2] Substituted hydroxycyclobutanes are observed in natural products, such as tsugicoline-A derivatives and pasteuresins, two classes of antimicrobial metabolites isolated respectively from Echinodontium tzugicola and Agrocibeaegerita sp.[3] 2-Alkyloxy- and 2-aryloxy-cyclobutanones have been used as intermediates in the synthesis of anti-tumor agents of the gilvocarcins family,[4] the sterol synthesis inhibitors zaragozic acids,[5] anti-HIV and anti-HBV molecules such as IB-0020866 and BMS-200475 (Entecavir®)[7] and biologically active pseudo-nucleosides including aristeromycin and carbovir.[8] More specifically, benzyloxy cyclobutanones have been used in straightforward syntheses of cyclobutane amino acids,[9] cyclic eptenones,[10] tetrahydropyranyl,[11] spiro cyclobutane derivatives,[12] and cyclobutane amino alcohols[13] as summarized in Figure 1. However, despite their broad utility, only a few synthetic methods are available for the direct preparation of cyclobutanones bearing an oxygen function in the 2-position; these consist mainly of stoichiometric, multistep procedures including the direct reaction of 1,2-bis(trimethyldisilyloxy)cyclobutene with benzyl alcohol in concentrated hydrochloric acid,[14a] 2,2-dialkoxy-cyclobutanol reaction with benzyl bromide in basic conditions,[14b] and inter[14c] or intramolecular[14d] [2+2] ketene-cyclization reactions with alkenes.

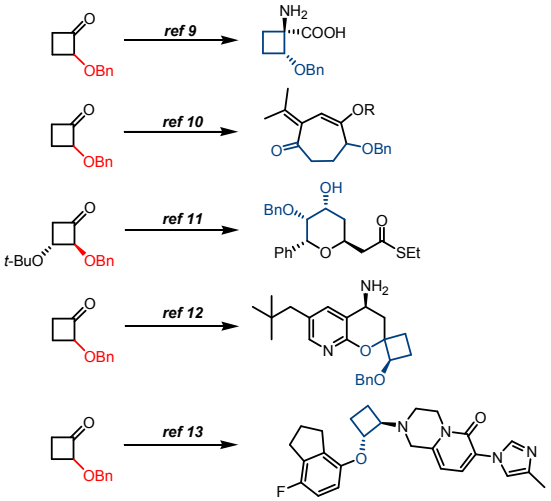

Figure 1. Selected examples of synthetic transformations of benzyloxycyclobutanones.

We recently reported a series of synthetic protocols based on the use of 2-hydroxycyclobutanone **1a** as the starting material for single step synthesis of libraries of α-amino cyclobutanones,[15,16] and cyclobutanone amino acids.[17] Pursuing our interest in this area,[18] we now report on our studies of the reactions of **1a** with oxygen nucleophiles in the form of diversely functionalized benzylic alcohols, leading to a simple and useful synthetic access to a panel of 2-benzyloxycyclobutanones as well as an unexpected access to novel dimers thereof having a 1,6-bis(alkoxy)-2,7-dioxatricyclo[6.2.0.03,6]decane skeleton.

Results and discussion

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Electronic Supplementary Information (ESI) containing reaction procedures, copies of ^{1}H and ^{13}C NMR spectra, X-Ray analysis and DFT calculations are available: See DOI: 10.1039/x0xx00000x

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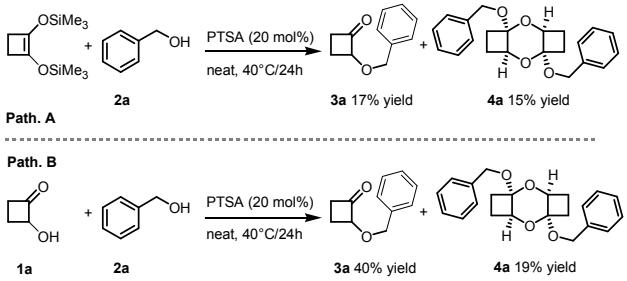
Synthesis of 2-benzyloxycyclobutanones

2-Benzyloxycyclobutanone **3a** (Scheme 1 Path. A) has previously been prepared from 1,2-bis(trimethyldisilyloxy)cyclobutene and benzyl alcohol **2a** in the presence of HCl.[14a] However this procedure is incompatible with many acid sensitive aryl functions and is difficult to control on small scale: reactions often give low chemical yields and the recovery of the unreacted cyclobutanone **1a** is inefficent.[14a-c] We felt that this transformation ought to proceed in the presence of a catalytic amount of acid, so we planned a set of experiments aimed at reducing the experimental complexity and the risks related to the use of dry HCl, with a view to establishing a robust procedure which operates on preparative scale.

In a preliminary study, the reaction of 1,2-bis(trimethyldisilyloxy)cyclobutene with benzyl alcohol **2a** in the presence of PTSA (20 mol %) at 40 °C for 24 h was sluggish. The target 2-benzyloxycyclobutanone **3a** was isolated in only 17% yield and a second reaction product, identified as 1,6-bis(benzyloxy)-2,7-dioxatricyclo[6.2.0.03,6]decane **4a**, was obtained in 15% yield (Scheme 1, Path. A). A comparative experiment was carried out using **1a** as the starting material. After 48 h, **3a** was isolated in an improved 40% yield and the dioxatricyclodecane 4a was obtained in 19% (Scheme 1, Path. B).



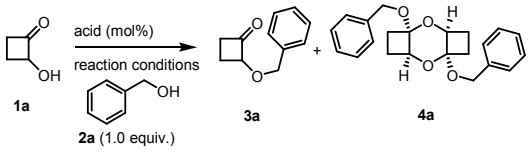
Scheme 1. Acid-catalyzed reaction of benzyl alcohol with 1,2-bis(trimethyldisilyloxy)cyclobutene and with 2-hydroxycyclobutanone.

This encouraging result was the starting point for a screening of a number of reaction parameters, including: solvents, temperature, reaction stoichiometry, catalyst identity, catalyst loading and reaction times in the reaction of cyclobutanone 1a with benzyl alcohol **2a.**

As reported in Table 1, when the reaction was carried out using PTSA (20 mol %) at 40 °C in toluene or *n*-hexane (entries 1 and 2) poor yields of **3a** were observed although in the latter solvent dioxatricyclodecane **4a** was formed in 25% yield. The use of ether or ester solvents (1,4-dioxane, THF, EtOAc) gave similarly disappointing results (entries 3-5), while in MeCN the reaction did not proceed at all (entry 6); starting materials were recovered unchanged after 48 hours reaction. Better results were achieved when the reaction was carried out in CH_2Cl_2 (entry 7), from which compound **3a** was isolated in 28% yield, accompanied by small amounts (5%) of **4a**. when the catalyst loading was increased to 30 mol %, **3a** was isolated in a much improved 79% while traces of **4a** were observed (entry 8). The use of 30 mol% of other sulfonic acids, CSA and MSA, was less efficient (entries 9 and 10) and the weaker acid

Table 1. Screening of reaction conditions leading to the optimization of the preparation of 2-benzyloxycyclobutanone **3a.**[a]

Entry	Catalyst/mol%	Solvent/T°C	Yield **3a**[b]	Yield **4a**
1	PTSA/20	toluene/40	9	3
2	PTSA/20	*n*-hexane/40	9	25
3	PTSA/20	dioxan/40	6	-
4	PTSA/20	THF/40	4	7
5	PTSA/20	EtOAc/40	8	-
6	PTSA/20	MeCN/40	-	-
7	PTSA/20	CH_2Cl_2/40	28	5
8	PTSA/30	CH_2Cl_2/40	88	3
9	CSA/30	CH_2Cl_2/40	52	16
10	MSA/30	CH_2Cl_2/40	41	4
11	PPTS/30	CH_2Cl_2/40	-	-
12	TFA/30	CH_2Cl_2/40	24	10
13	H_2SO_4/30	CH_2Cl_2/40	72	5
14	AMB-15[c]	CH_2Cl_2/40	86	*traces*
15	BF_3-OEt_2/20	CH_2Cl_2/-20	4	-
16	$TiCl_4$/20	CH_2Cl_2-20	-	-
17	$Cu(OTf)_2$/20	CH_2Cl_2/25	-	-
18	$SnCl_4$/20	CH_2Cl_2/25	-	-



a) Reaction conditions: in a 5 mL vial, cyclobutanone 1a (50 mg) BnOH (1.0 equiv.) and the selected acid and solvent (1 mL), were stirred at the indicated temperatures and periodically checked by GC-MS. c) Yields were determined by weighing after isolation using flash chromatography. c) AMB-15 loading was 0.2 g AMB-15/mmol 1a. See ESI for AMB-15 loading and recycling.

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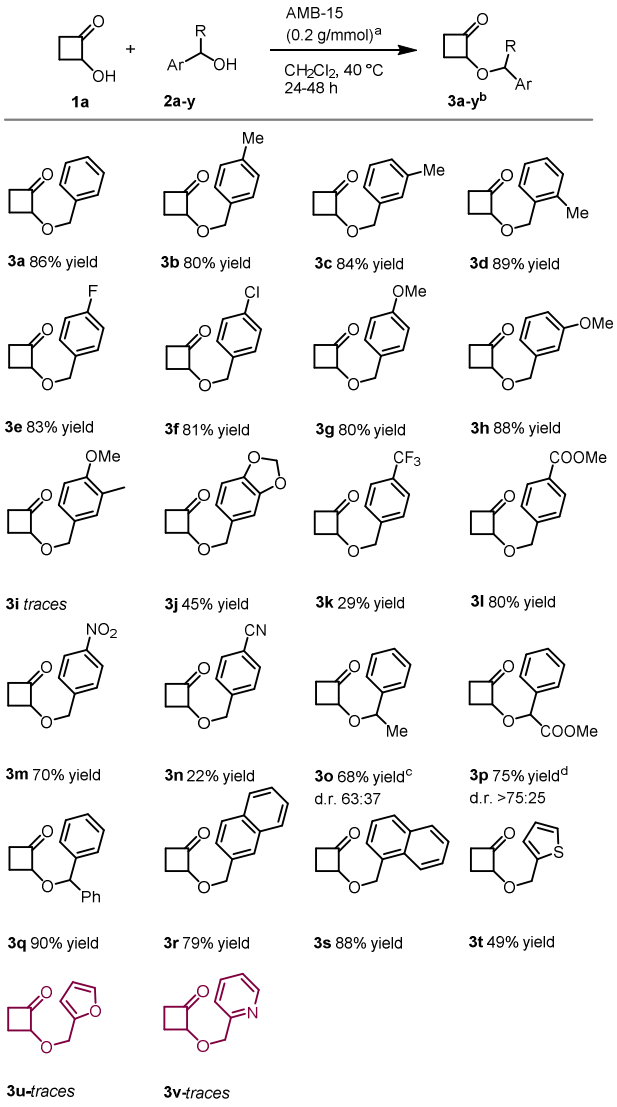
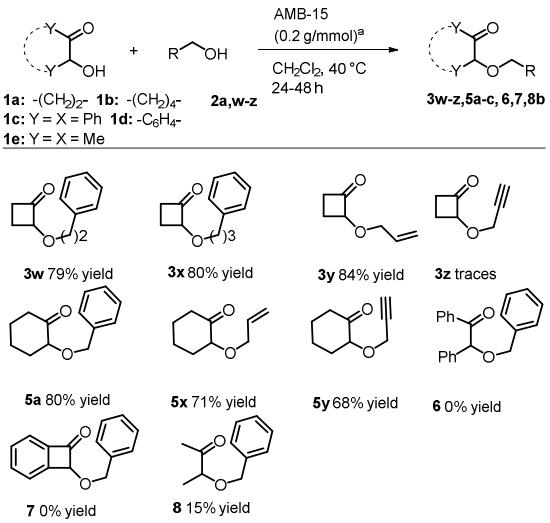
PPTS was ineffective (entry 11). Employment of TFA gave poor results (entry 12), whereas H_2SO_4 permitted formation of **3a** in 72% yield with only traces of **4a** being observed. Finally, the best result was obtained using Amberlist-15 (AMB-15)[19] as the catalyst, which afforded **3a** in 86% yield and only traces (<5%) of **4a** (entry 13). Selected Lewis acids BF_3-OEt_2, $TiCl_4$, $Cu(OTf)_2$ or $SnCl_4$ were evaluated but were essentially ineffective (entries 14-17). From the data collected in Table 1, the use of AMB-15 as the catalyst and dichloromethane as the solvent were considered as being optimal for the preparation of **3a** and these conditions were retained for further investigations of the reaction scope.



Scheme 2. Scope of benzyloxycyclobutanones synthesis from cyclobutanone **1a**. [a] Reaction conditions: in a vial, cyclobutanone **1a** (50 mg) BnOH **2a** (1.0 equiv.), AMB-15 (0.2 g AMB-15/mmol of **1a**) in CH_2Cl_2 (1 mL) were stirred at 40 °C for 48 h. [b] Yields were determined by weighing after isolation using flash chromatography. [c] Determined by ^{1}H-NMR analysis. [d] Determined by ^{1}H-NMR and GC-MS analysis.



Scheme 3. AMB-15 catalyzed synthesis of α-alkyloxyketones. [a] Reaction conditions: in a vial, ketones **1a-e** (0.58 mmol), alcohols (1.0 equiv.), AMB-15 (0.2 g AMB-15/mmol **1a-e**) in CH_2Cl_2 (1 mL) were stirred at 40 °C for 48 h. [b] Yields were determined by weighing after isolation using flash chromatography.

The reaction scope was assessed using a panel of substituted benzylic and related alcohols **2a-v**. Each alcohol was reacted with cyclobutanone **1a** in the optimized conditions established above to afford the corresponding 2-alkyloxycyclobutanones **3a-v** as illustrated in Scheme 2 starting from aryl-substituted benzyl alcohol derivatives **2b-v**. With the exception of **2i**, the (aryl-substituted)benzyl alcohols **2a-n** reacted efficiently, allowing isolation of the corresponding cyclobutanones **3a-n** in moderate to excellent yields. Notably, the presence of ring-activating groups such as *o*-, *m*- or *p*-Me or *m*- or *p*-OMe, did not influence the reaction and the corresponding dioxatricyclodecanes were detected in less than 8% yield, if at all. Likewise, *p*-F and *p*-Cl substituents were easily accommodated. Alcohols **2k** and **2n**, bearing a *p*-CF3 and a *p*-CN substituent respectively, gave low yields of the cyclobutanones **3k** (29%) and **3n** (<12%), principally due to the competitive formation of the dioxatricyclodecanes *syn*-**4k**, (70% yield) and **4n** (88% yield, (*cis/trans* 9:1), respectively. With the ring-disubstituted benzyl alcohol **2i** only traces of the adduct **3i** were formed, despite the complete consumption of alcohol substrate. This observation can be explained by the postulate that **2i** forms a stabilized carbocation species that undergoes facile electrophilic aromatic substitution of a second equivalent of **2i**, as previously observed by other authors.[20] With α-substituted benzyl alcohols **2o-q**, the reaction was equally efficient (yields 68-90%) although the diastereoselectivity was modest. Reactions with naphthylmethyl alcohols **2r** and **2s** also proceeded in good yields, while α-(hydroxylmethyl)thiophene **2t** gave a more modest 49% yield of **3t**. Finally, reactions with heterocyclic alcohols **2u** and **2v** were ineffective, providing a large number of unidentified products which included only traces of the target cyclobutanones **3u** and **3v**.

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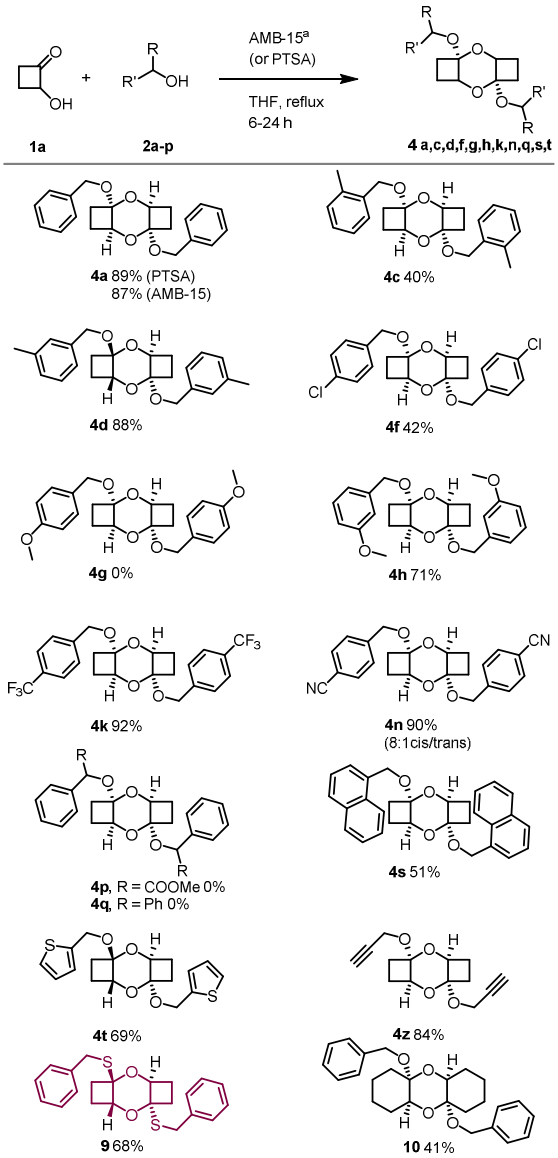
The above-described protocol was extended to the reaction of **1a** with other primary alcohols 2-phenylethanol, 3-phenylpropano, allylic and propargylic alcohols (**2w-z**), as shown in Scheme 3. The reactions with the first three reagents gave the corresponding ethers **3w-y** in high yields but failed with **2z**. We also examined the reaction of primary alcohols with other hydroxyketones (Scheme 3). Hydroxycyclohexanone **1b** reacted with alcohols **2a**, **2x** and **2y** to provide the corresponding ethers in good yields.[21] On the other hand, the reaction of benzyl alcohol **2a** with other α-hydroxyketones was unproductive: 3-hydroxy-2-butanone **1e** provided the adduct **8** in only 15% while 1,2-diphenyl-2-hydroxy ketone was **1d** and the cyclobutabenzene **1e** were recovered unchanged after 48 h reaction time.

Synthesis of dioxatricyclodecanes

The formation of compounds with the rare 1,6-bis(alkoxy)-2,7-dioxatricyclo[6.2.0.03,6]decane skeleton in several of the above described experiments retained our attention and we endeavored to optimize their synthesis. Intuitively, we considered that these compounds had appeared from a tandem reaction process implicating the acid-mediated dimerization of the initially-formed alkoxycyclobutanone adducts **4**. To confirm this postulate we repeated the reaction of cyclobutanone **1a** with the alcohol **2a** in CH_2Cl_2 at 40 °C in the presence of a stoichiometric amount of PTSA. In these conditions, tricyclic compound **4a** was isolated in 27% yield accompanied by 62% of benzyloxycyclobutanone **3a** after 48 h. The employment of 0.5 and 0.7 equivalents of PTSA resulted in lower conversions to the dimeric adduct **4a** (6:1-7:1 mixtures of **3a** and the dimerization product **4a** respectively). In the initial screening experiments reported in Table 1, we had noted that (despite the low conversion) non-chlorinated solvents had favoured the formation of tricyclic compound **4a**, rather than **3a**. When **1a** and **2a** were reacted in the presence of 30 mol % of PTSA in refluxing toluene, results were erratic; however, the use of THF as solvent at 65 °C provided compound **4a** in a gratifying 89% yield after 24 h reaction time. The use of AMB-15 (0.2 g/mmol loading) in the same conditions gave compound **4a** in an equally satisfying 86% yield. An advantage of employing AMB-15 was that its recovery at the end of the reaction time was trivial and it could be easily reused in more than four catalytic cycles without significant erosion of the chemical yield of **4a** (see ESI). We therefore retained AMB-15 for further experiments. In order to examine the scope of the dioxatricyclodecane synthesis, benzylic alcohols **2c,d,f,g,h,k,n,p,q,s,t** and propargyl alcohol **2z** were each reacted with cyclobutanone **1a** in THF, in the presence of AMB-15 as the catalyst. As shown in Scheme 4, moderate yields of compound **4c** (40%) 4f (42%) and **4s** (51%), were isolated after 24 h reaction accompanied by only small amounts (<10%) of the corresponding 2-arylmethylcyclobutanone. Excellent yields of compounds **4k** (92%) and **4n** (90% 80:20 mixture of two diastereoisomers) were obtained with no traces of a corresponding 2-arylmethylcyclobutanone in the ^{1}H-NMR spectra of crude reaction mixtures. High yields of the tricyclic adducts **4d** (88%) and **4h** (71%) were also obtained. Curiously, the synthesis of compound **4g** failed despite several attempts. The reaction of alcohols **2p** and **2q** gave only the cyclobutanones **3p** and **3q** after 48 h reaction time, probably due to steric effects. Finally, tricyclic derivatives **4t** (69%) and **4z** (84%) were isolated in good yields. A reaction between benzylthiol and cyclobutanone 1a was conducted in the same conditions and provided 1.6-bis(benzylthio)-2,7-dioxatricyclo[6.2.0.03,6]decane **9** in 68% yield, indicating that this protocol is amenable to reactions involving other nucleophiles. The tandem 2-hydroxyketone functionalization-cyclization process was also examined with compound **1b** and **2a**, leading to the *syn*-tricyclic dioxine **10** in 41% yield.[22]



Scheme 4. AMB-15 catalyzed synthesis of dioxatricyclodecanes a) Reaction conditions: in a vial, cyclobutanone **1a** (0.58 mmol) alcohol **2a** (1.0 equiv.), AMB-15 (0.2g of AMB-15/mmol of **1a** in THF (2 mL) were stirred at 65° C for 48h. b) Yields of **4a** were determined by weighting after isolation using flash chromatography.

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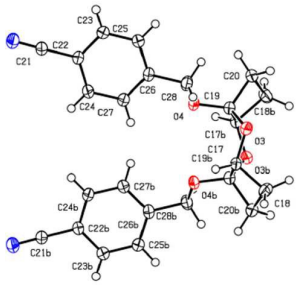


Figure 2. ORTEP representation (ellipsoid probability 50%) of the molecular structure *syn*-**4n**, as determined by single crystal X-ray diffraction analysis. For full details see the ESI).

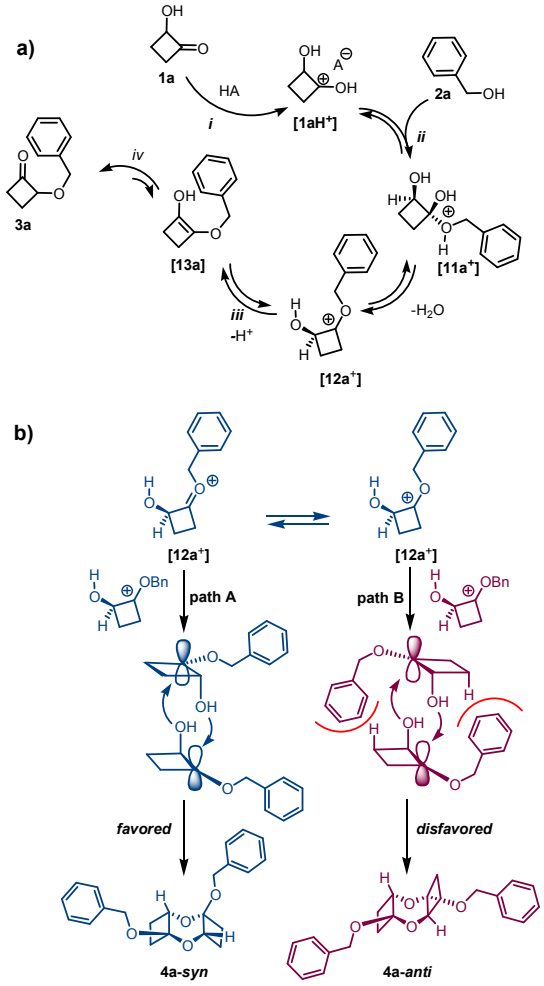
The relative configuration of the major diastereoisomer of dioxatricyclodecane **4n** was determined by single crystal X-ray analysis and displayed a *syn*-relative configuration. On the basis of the similarities in the ^{1}H and ^{13}C-NMR spectroscopic signatures it is proposed by extension that the same configuration pattern prevails throughout the series of compounds **4a,c,d,f,h,k,s,z** of this work (Figure 2, see ESI for details). The *anti*-configuration was attributed to compounds **4d**, **t** and compound **9**.

DFT calculations and mechanistic aspects

In order to rationalize the mechanistic aspects of the acid promoted functionalization of 2-hydroxyl-cyclobutanone (giving 3) as well as the tandem ketone-functionalization/dimerization process (giving 4), a series of theoretical calculations were carried out at DFT level. The mPW1PW functional[23] was chosen, paralleled by a split valence plus polarization basis sets in the newer formulation by Wiegend and Ahlrichs (Def2SVPP)[24,25] as implemented in Gaussian 09.20 The proposed reaction mechanisms based on the experimental results and the DFT calculations are summarized in Scheme 5. The DFT-optimized structure of 2-hydroxycyclobutanone **1a** shows an elongated C(O)–C(OH) bond distance (1.524 Å), in agreement with the ring strain associated with a four-membered cycle.[1]

Although experimental data are not available for **1a**, this calculated bond distance is in good agreement with those observed in the X-ray diffraction analyses of (1'*R*,2*R*,2'*S*)-2-(2-chloro-1-hydroxycyclohexyl)-2-ydroxycyclobutanone and the corresponding bromo-analogue [C(O)-C(OH), which are 1.544 Å and 1.548 Å, respectively; CCDC codes WACBAN and WAJZUE).[26] When **1a** is O-protonated to give [**1a**H^{+}] (Scheme 5a, step i), the C–C distance undergoes a remarkable shortening (to 1.472 Å) accompanied by an increase in the partial natural charge calculated on the C1 carbon (QC1 = +0.569 and +0.612 |e| for **1a** and [**1a**H^{+}], respectively). Accordingly, the Kohn-Sham unoccupied molecular orbital (KS-LUMO) is mainly constituted by the 2pz atomic orbital (AO) localized on this carbon atom, rendering it suitable for a nucleophilic attack by benzyl alcohol **2a** (or a related derivative), according to step ii of the same scheme. Elimination of water from the resulting dihydroxycyclobutane cation [**11**a^{+}] would lead to cationic intermediates [**12**a^{+}] then neutral **13a** intermediates (see also Figure 3). An examination of the natural charge distribution in substituted 1-hydroxy-2-benzyloxycyclobutene structures **12a**, **b**, **g**, **k**, **n**, showed that the nature of the donor substituents in the 4-position of the phenyl ring affects the charges on the four-membered carbocyclic ring. In particular, donor substituents (**13b**, **13g**) increase the positive charge on the benzyloxy-substituted carbon atom (QC1 = +0.232 and +0.233 |e|, respectively), while electron-withdrawing substituents (**13k**, **13n**) induce the opposite effect (QC1 = +0.227 and +0.225 |e|) with respect to the charge calculated on **3a** QC1 = +0.231 |e|).

A comparison of the DFT-optimized geometry for compounds [**12a**$^{+}$], [**12b**$^{+}$], [**12g**$^{+}$], [**12k**$^{+}$], and [**12n**$^{+}$] showed that methyl and methoxy substituent groups induce a weakening in the



Scheme 5. a) Proposed mechanistic path for benzylic functionalization of 2-hydroxylbutanone **1a**. b) Proposed intermolecular dimerization process and stereochemical outcome. Only those hydrogen atoms involved in the reactions have been represented for clarity.

benzyl C–O bond, testified by a significant elongation, while CF3 and CN groups cause the opposite effect (1.523, 1.531, 1.527, 1.497 and 1.489 Å for [**12a**$^{+}$], [**12b**$^{+}$], [**12g**$^{+}$], [**12k**$^{+}$] and [**12n**$^{+}$], respectively). The calculated bond lengthening for [**6b**$^{+}$] and [**12g**$^{+}$] could in principle render these cations prone to hydrolysis. Since the postulated cations [**12**$^{+}$] and the

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unsaturated neutral species **13** can be interconverted, the electronic factors which increase the yields of step iii result in a lowering of the yields of step iv. Accordingly, electron-withdrawing substituents on the benzyl alcohol result in quite low yields in step iii to give **3**, but determine the highest conversions in step iv, while an opposite trend is observed when donor *p*-substituents are implicated.

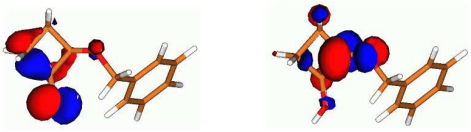
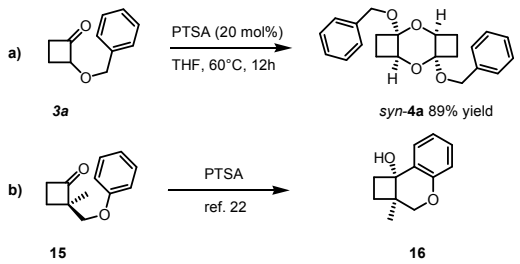


Figure 3. Isosurface drawings of KS-HOMO–2 (left) and LUMO (right) calculated for **3a**. Contour value = 0.05 e.

The enol [**13a**] plays a fundamental role in the reaction mechanism leading to **3a**. Indeed, cyclobutanones bearing a 2-benzyloxy substituent are known to undergo a rapid intramolecular Friedel-Crafts ring-closure reaction, leading to cyclobutachromanes as previously reported (Scheme 6).[27] At no point in the present work did we encountered such reactivity and we believe that this observation is closely related to the predominance of the enol species **12a** which is not conducive to electrophilic ring closure. The proposed mechanism excludes the involvement of a benzyl carbocation, which could react with the hydroxyl group of **1a**. On the basis of the successful isolation of the compounds 3k-m bearing an electron withdrawing groups (*p*-CF_3, *p*-COOMe or *p*-NO_2) which should disfavor the formation of a benzyl carbocation. To support this premise, alcohols **2a**, was treated with PTSA (30 mol %) in the presence of a carbocation scavenger species (anisole)[28] in dichloromethane at 40 °C, for 48 h. After that time, no traces of the corresponding benzyl-aryl ethers was observed.



Scheme 6. a) Acid catalyzed dimerization of 2-benzyloxycyclobutanone **3a** into adduct **4a.** b) Acid-catalyzed cyclization of 2-aryloxycyclobutanones **15** into cyclobutachromanes **16**.

The predominant *syn*-stereochemistry observed for the majority of the dimeric compounds **4** is explained in Scheme 5b. Path A represents a suitable molecular disposition to promote the dimerization reaction, in which steric effects are minimized by the relative orientation of the benzyloxy substituents on the four-membered ring carbocation [**12a**$^+$].These effects are more prevalent in Path B, in which we assume that a reduced interaction limits the formation of a predominant anti-configuration for the series.

Conclusions

In conclusion, we have developed acid-mediated, solvent-dependent, chemoselective and environmentally-friendly protocols for the synthesis of either 2-benzyloxycyclobutanones or novel dioxatricyclodecanes in good to excellent yields, starting from 2-hydroxycyclobutanone and diversely-functionalized benzylic alcohols. The former products are obtained using catalytic amounts of PTSA or Amberlyst-15® in dichloromethane, while the latter are prepared using Amberlyst-15® in THF in a tandem benzyloxy-functionalization/dimerization process. These reactions can easily be performed on milligram to gram scale and the resin-bound catalyst can be recovered by simple filtration and reused several times without significant loss of its catalytic properties. DFT calculations allowed insight into the electronic effects at play in these reactions and rationalized the experimental results.

Conflicts of interest

There are no conflicts to declare.

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Experimental section

Unless stated otherwise, syntheses of compounds **3a-v** were performed at 40 °C and syntheses of compounds **5a-v** were performed at 65 °C.

Commercially available reagents were used as received unless otherwise noted. Alcohols **2a,c,d,h,p,u,y,z** were purchased from Aldrich. The acids used in this work were purchased from Aldrich or Alfa-Aesar and were used as received.

^{1}H NMR spectra were recorded on 400 and 500 MHz Varian spectrometers at 27 °C using $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded at 100 and 125 MHz at 27 °C using $CDCl_3$ as solvent. Chemical shifts (δ) are given in ppm. Coupling constants (*J*) are reported in Hz. Infrared spectra were recorded on a FT-IR Bruker Equinox-55 spectrophotometer and are reported in wavenumbers. Low resolution mass spectra analyses were recorded on an Agilent-HP GC-MS (E.I. 70 eV). High-resolution mass spectra (HRMS) were obtained using a Bruker high-resolution mass spectrometer in fast atom

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bombardment (FAB+) ionization mode or were acquired using an Bruker micrOTOF-Q II 10027.

Analytical thin layer chromatography was performed using 0.25 mm Aldrich silica gel 60-F plates. Flash chromatography was performed using Merck 70-200 mesh silica gel.

Yields refer to chromatographically and spectroscopically pure materials.

Density Functional Theory (DFT) calculations were performed with the commercial suite of software Gaussian 09.[26] All calculations were carried out with the hybrid Generalized Gradient Approximation (GGA) mPW1PW functional[17] and the full-electron split valence plus polarization basis sets in the Def2SVPP formulation[24,25] for all atomic species. NBO[25] populations were calculated at the optimized geometries, whose nature was verified by harmonic frequency calculations (no negative frequencies with module larger than 15 cm^{-1} were found). The results of the calculations were examined with GaussView 5.0.9[26] and Molden 5.3[27] programs.

General procedure for the synthesis of cyclobutanones 3a-v. To a solution of benzyl alcohol **2** (0.46 mmol) and 2-hydroxycyclobutanone **1a** (39.8 mg, 0.46 mmol) in CH_2Cl_2, (1 mL), *p*-toluenesulfonic acid (17 mg, 0.09 mmol) was added. The reaction mixture was stirred at 40 °C for 48 h and checked by GC-MS analysis until completion. The reaction solution was charged on a silica gel column and chromatographed (flash chromatography, 90:10 hexanes/diethyl ether).

2-Benzyloxy-cyclobutanone 3a. (flash chromatography, 90:10 hexanes/diethyl ether), 88 % yield (69 mg). FTIR (neat) ν: 3038, 2926, 2867, 1788, 1458, 1396, 1148, 1401 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.46-7.25 (m, 5H), 4.83-4.67 (m, 2H), 4.62 (d, *J* = 11.7 Hz, 1H), 2.87-2.62 (m, 2H), 2.31 (ddd, *J* = 20.6, 9.8, 5.4 Hz, 1H), 1.96 (qd, *J* = 10.6, 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.5, 137.1, 128.4, 128.0, 86.9, 72.1, 39.3, 19.6. Spectroscopic data are in accordance with those previously reported.[9]

2-(4-Methyl-benzyloxy)-cyclobutanone 3b. flash chromatography (90:10 hexanes/diethyl ether), 80 % yield (81 mg). FTIR (neat) ν: 2868, 2254, 1789, 1523, 1143 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.28-7.20 (m, 2H), 7.16 (d, *J* = 7.8 Hz, 2H), 4.75-4.66 (m, 2H), 4.58 (d, *J* = 11.6 Hz, 1H), 2.81-2.67 (m, 2H), 2.34 (s, 3H), 2.29 (dtd, *J* = 11.0, 10.0, 5.1 Hz, 1H), 1.93 (ddd, *J* = 21.3, 10.3, 7.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 206.6, 137.7, 134.0, 129.1, 128.1, 86.8, 71.9, 39.3, 21.1, 19.6; HRMS (ESI): calcd for $C_{12}H_{14}NaO_2$: 213,0891 $(M+Na)^+$, found: 213.0884.

2-(3-Methyl-benzyloxy)-cyclobutanone 3c. flash chromatography (90:10 hexanes/diethyl ether), 84 % yield (85 mg). FTIR (neat) ν: 2984, 2870, 1789, 1532, 1143, 904 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21 (dd, *J* = 22.6, 15.1 Hz, 1H), 7.12 (dd, *J* = 15.6, 7.5 Hz, 3H), 4.72 (m, 2H), 4.58 (d, *J* = 11.6 Hz, 1H), 2.83-2.57 (m, 2H), 2.34 (s, 3H), 2.30 (ddd, *J* = 20.8, 10.2, 5.1 Hz, 1H), 1.94 (qd, *J* = 10.4, 7.8 Hz, 1H).; ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.5, 138.0, 137.0, 128.7, 128.7, 128.3, 125.0, 86.9, 72.0, 39.2, 21.2, 19.5; HRMS (ESI): calcd for $C_{12}H_{14}NaO_2$: 213,0891 $(M+Na)^+$, found: 213.0878.

2-(2-Methyl-benzyloxy)-cyclobutanone 3d. flash chromatography (90:10 hexanes/diethyl ether), 89 % yield (90 mg). FTIR (neat) ν: 2982, 2874, 1789, 1534, 1160, 1027, 910 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.31 (d, *J* = 7.1 Hz, 1H), 7.21 (dd, *J* = 10.6, 4.0 Hz, 2H), 7.17 (dd, *J* = 6.1, 3.5 Hz, 1H), 4.60 (d, *J* = 11.5 Hz, 1H), 2.82-2.62 (m, 1H), 2.83-2.67 (m, 2H), 2.35 (s, 3H), 2.29 (ddd, *J* = 20.7, 10.5, 4.9 Hz, 1H), 1.93 (qd, *J* = 10.4, 7.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 206.7, 137.0, 135.0, 130.3, 128.9, 128.2, 125.7, 86.9, 70.5, 39.2, 19.5, 18.8; HRMS (ESI): calcd for $C_{12}H_{14}NaO_2$: 213,0891 (M+Na), found: 213.0881.

2-(4-Fluoro-benzyloxy)-cyclobutanone 3e. flash chromatography (90:10 hexanes/diethyl ether), 83 % yield (93 mg). FTIR (neat) ν: 3010, 2962, 2933, 2869, 1788, 1604, 1512, 1222, 1150, 1061, 910, 825 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (dd, *J* = 8.3, 5.6 Hz, 2H), 7.03 (t, *J* = 8.7 Hz, 2H), 4.82-4.61 (m, 2H), 4.58 (d, *J* = 11.5 Hz, 1H), 2.90-2.57 (m, 2H), 2.32 (ddd, *J* = 20.9, 9.9, 5.2 Hz, 1H), 1.95 (qd, *J* = 10.5, 7.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 206.4, 163.7, 132.9, 129.8 (d, *J* = 8.1 Hz), 115.3 (d, *J* = 21.5 Hz), 86.9, 71.3, 39.3, 19.5; HRMS (ESI): calcd for $C_{11}H_{11}FNaO_2$: 217,0641 $(M+Na)^+$, found: 217,0649.

2-(4-Chloro-benzyloxy)-cyclobutanone 3f. flash chromatography (90:10 hexanes/diethyl ether), 81 % yield (99 mg). FTIR (neat) ν: 3036, 2879, 1786, 1496, 1267, 908, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.33-7.09 (m, 4H), 4.75-4.55 (m, 2H), 4.50 (d, *J* = 11.8 Hz, 1H), 2.82-2.51 (m, 2H), 2.24 (dtd, *J* = 11.1, 9.9, 5.2 Hz, 1H), 1.87 (ddd, *J* = 21.4, 10.3, 7.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 206.3, 135.6, 133.7, 129.2, 128.5, 87.0, 71.2, 39.3, 19.5; HRMS (ESI): calcd for $C_{11}H_{11}ClNaO_2$: 233,0345 $(M+Na)^+$, found: 233,0348.

2-(4-Methoxy-benzyloxy)-cyclobutanone 3g. flash chromatography (90:10 hexanes/diethyl ether), 80 % yield (95 mg). FTIR (neat) ν: 2930, 2868, 2254, 1792, 1625, 1519, 1328, 1167, 1126, 1065, 1017, 911, 822 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.37-7.18 (m, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.74-4.66 (m, 2H), 4.56 (d, *J* = 11.3 Hz, 1H), 3.81 (s, 1H), 2.81-2.62 (m, 2H), 2.29 (ddd, *J* = 20.8, 9.8, 5.3 Hz, 1H), 1.93 (ddd, *J* = 21.3, 10.3, 7.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 206.9, 161.3, 159.7, 129.9, 114.0, 86.9, 71.9, 55.4, 39.5, 19.8; HRMS (ESI): calcd for $C_{12}H_{14}NaO_3$: 229.0841 $(M+Na)^+$, found: 229.0843.

2-(3-Methoxy-benzyloxy)-cyclobutanone 3h. flash chromatography (90:10 hexanes/diethyl ether), 88 % yield (105 mg). FTIR (neat) ν: 2930, 2870, 1790, 1630, 1519, 1340, 1167, 1128, 1065, 1015 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.25 (dd, *J* = 9.4, 6.3 Hz, 1H), 6.92 (d, *J* = 7.6 Hz, 2H), 6.89-6.78 (m, 1H), 4.78-4.65 (m, 2H), 4.59 (d, *J* = 11.9 Hz, 1H), 3.80 (s, 4H), 2.84-2.58 (m, 2H), 2.30 (dtd, *J* = 15.1, 9.9, 5.1 Hz, 1H), 1.95 (qd, *J* = 10.4, 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ: 206.4, 159.7, 138.7, 129.4, 120.1, 113.6, 113.1, 86.9, 71.8, 55.1, 39.2, 19.5;

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HRMS (ESI): calcd for $C_{12}H_{14}NaO_3$: 229.0841 $(M+Na)^+$, found: 229.0847.

2-(Benzo[1,3]dioxol-5-ylmethoxy)-cyclobutanone 3j. flash chromatography (90:10 hexanes/diethyl ether), 45 % yield (58 mg). FTIR (neat) ν: 2879, 2353, 1786, 1495, 1444, 1249, 1143, 1034, 925 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 6.86 (s, 1H), 6.79 (q, *J* = 7.9 Hz, 2H), 5.95 (s, 2H), 4.75-4.67 (m, 1H), 4.65 (d, *J* = 11.4 Hz, 1H), 4.52 (d, *J* = 11.4 Hz, 1H), 2.91-2.65 (m, 2H), 2.30 (ddd, *J* = 20.8, 9.8, 5.3 Hz, 1H), 1.94 (ddd, *J* = 21.3, 10.5, 7.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 206.6, 147.8, 147.4, 131.1, 121.8, 108.7, 108.0, 101.0, 86.6, 76.4, 71.9, 39.3, 19.6; HRMS (ESI): calcd for $C_{12}H_{12}NaO_4$: 243,0633 $(M+Na)^+$, found: 243,0639.

2-(4-Trifluoromethyl-benzyloxy)-cyclobutanone 3k. flash chromatography (90:10 hexanes/diethyl ether), 29 % yield (41 mg). FTIR (neat) ν: 2930, 2879, 1776, 1622, 1421, 1325, 1168, 1124, 1069 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 8.1 Hz, 2H), 7.47 (d, *J* = 8.0 Hz, 2H), 4.82 (d, *J* = 12.3 Hz, 1H), 4.77-4.72 (m, 1H), 4.68 (d, *J* = 12.3 Hz, 1H), 2.86-2.67 (m, 2H), 2.42-2.28 (m, 1H), 1.99 (dtd, *J* = 18.0, 10.3, 7.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 206.3, 141.5, 130.3 (q, *J* = 32.2 Hz), 128.0, 125.5 (d, *J* = 3.2 Hz), 87.4, 71.3, 39.6, 19.7; HRMS (ESI): calcd for $C_{12}H_{11}F_3NaO_2$: 267.0609 $(M+Na)^+$, found: 267.0611.

4-(2-Oxo-cyclobutoxymethyl)-benzoic acid methyl ester 3l. flash chromatography (90:10 hexanes/diethyl ether), 80% yield (108 mg). FTIR (neat) ν: 2916, 1789, 1721, 1283, 908 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.05-8.00 (m, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 4.82 (dd, *J* = 12.4, 4.2 Hz, 1H), 4.78-4.71 (m, 1H), 4.68 (dd, *J* = 12.5, 4.1 Hz, 1H), 3.91 (s, 3H), 2.84-2.71 (m, 2H), 2.40-2.29 (m, 1H), 1.99 (td, *J* = 10.5, 7.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 206.1, 166.7, 142.3, 129.6, 127.4, 87.2, 71.3, 52.0, 39.3, 19.5; HRMS (ESI): calcd for $C_{12}H_{12}NaO_4$: 257,0790 $(M+Na)^+$, found: 257.0785.

2-(4-Nitro-benzyloxy)-cyclobutanone 3m. flash chromatography (90:10 hexanes/diethyl ether), 70 % yield (89 mg). FTIR (neat) ν: 2954, 2858, 1789, 1605, 1519, 1348, 1150, 1065, 853, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ: 8.21 (d, *J* = 8.5 Hz, 2H), 7.53 (d, *J* = 8.4 Hz, 2H), 4.88 (d, *J* = 12.9 Hz, 1H), 4.78 (t, *J* = 8.7 Hz, 1H), 4.73 (d, *J* = 13.0 Hz, 1H), 2.90-2.66 (m, 2H), 2.40 (ddd, *J* = 15.0, 10.4, 5.2 Hz, 1H), 2.02 (td, *J* = 18.5, 10.5 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 206.0, 147.5, 144.7, 127.9, 123.6, 87.4, 70.6, 39.4, 19.5; HRMS (ESI): calcd for $C_{11}H_{11}NNaO_4$: 244,0586 $(M+Na)^+$, found: 244,0590.

2-(1-Phenyl-ethoxy)-cyclobutanone 3o. flash chromatography (90:10 hexanes/diethyl ether), 68 % overall yield (75 mg, d.r. = 63:37). *Major isomer*, FTIR (neat) ν: 2927, 2363, 2329, 1790, 1725, 1274, 1062, 731 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.41-7.22 (m, 5H), 4.79 (q, *J* = 6.5 Hz, 1H), 4.52 (t, *J* = 8.9 Hz, 1H), 2.75-2.53 (m, 2H), 2.18-1.99 (m, 1H), 1.83 (qd, *J* = 10.4, 8.1 Hz, 1H), 1.49 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 207.5, 142.8, 128.5, 127.8, 126.4, 85.8, 78.5, 39.1, 23.7, 20.2; HRMS (ESI): calcd for $C_{12}H_{14}NaO_2$: 213,0891 $(M+Na)^+$, found: 213.0878.

Minor isomer, FTIR (neat) ν: 2934, 2372, 1789, 1268, 1060, 756 cm^{-1} ^1H NMR (500 MHz, $CDCl_3$) δ: 7.40-7.22 (m, 5H), 4.60 (m, 2H), 2.74-2.56 (m, 2H), 2.35-2.19 (m, 1H), 2.00-1.82 (m, 1H), 1.48 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 205.4, 142.4, 128.5, 127.8, 126.4, 109.9, 85.5, 38.8, 23.5, 20.0; HRMS (ESI): calcd for $C_{12}H_{14}NaO_2$: 213,0891 $(M+Na)^+$, found: 213.0881.

(2-Oxo-cyclobutoxy)-phenyl-acetic acid ethyl ester 3p. flash chromatography (90:10 hexanes/diethyl ether), 75 % yield (102 mg). FTIR (neat) ν: 2998, 2894, 1813, 1790, 1342, 1210, 1021 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.50-7.44 (m, 1H), 7.44-7.33 (m, 4H), 5.36 (s, 1H), 4.11-4.03 (m, 1H), 3.40 (s, 3H), 2.41-2.32 (m, 2H), 2.23-2.11 (m, 1H), 1.81 (ddd, J = 10.4, 5.9, 2.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 206.9, 170.7, 130.1, 129.1, 128.7, 126.3, 81.2, 56.9, 30.8, 28.0, 20.7; HRMS (ESI): calcd for $C_{13}H_{14}NaO_4$: 257,0790 $(M+Na)^+$, found: 257.0783.

2-Benzhydryloxy-cyclobutanone 3q. flash chromatography (90:10 hexanes/diethyl ether), 90 % yield (132 mg). FTIR (neat) ν: 2982, 2363, 1783, 1489, 1329, 1127, 1066, 758, 703 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.44-7.11 (m, 10H), 5.71 (s, 1H), 4.71 (t, *J* = 8.7 Hz, 1H), 2.80-2.63 (m, 2H), 2.24 (dt, *J* = 17.7, 8.9 Hz, 1H), 1.98 (dd, *J* = 18.9, 10.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 206.5, 141.2, 141.0, 128.4, 128.4, 127.8, 127.7, 127.3, 127.0, 112.0, 85.6, 82.8, 39.2, 20.0; HRMS (ESI): calcd for $C_{17}H_{16}NaO_2$: 275,1048 $(M+Na)^+$, found: 275.1050.

2-(Naphthalen-2-ylmethoxy)-cyclobutanone 3r. flash chromatography (90:10 hexanes/diethyl ether), 79 % yield (103 mg). FTIR (neat) ν: 2865, 2363, 1802, 1786, 1509, 1396, 1140,1068, 771 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.07 (d, *J* = 8.4 Hz, 1H), 7.76 (dd, *J* = 16.3, 8.1 Hz, 2H), 7.45 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.43-7.38 (m, 2H), 7.37-7.32 (m, 1H), 5.19 (d, *J* = 11.7 Hz, 1H), 4.93 (d, *J* = 11.7 Hz, 1H), 4.72-4.61 (m, 1H), 2.74-2.53 (m, 2H), 2.13 (ddd, *J* = 20.9, 9.9, 5.2 Hz, 1H), 1.82 (qd, *J* = 10.3, 7.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 206.6, 133.7, 132.7, 131.7, 129.0, 128.4, 127.0, 126.4, 125.8, 125.1, 124.0, 86.9, 70.6, 39.3, 19.5; HRMS (ESI): calcd for $C_{15}H_{14}NaO_2$: 249,0891 $(M+Na)^+$, found: 249.0888.

2-(Naphthalen-1-ylmethoxy)-cyclobutanone 3s. flash chromatography (90:10 hexanes/diethyl ether), 88 % yield (115 mg). FTIR (neat) ν: 2989, 2363, 1790, 1076, 799 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 8.13 (d, *J* = 8.5 Hz, 1H), 7.82 (dd, *J* = 16.7, 8.1 Hz, 2H), 7.53 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.50-7.44 (m, 2H), 7.40 (dd, J = 8.1, 7.1 Hz, 1H), 5.24 (d, *J* = 11.7 Hz, 1H), 4.99 (d, *J* = 11.8 Hz, 1H), 4.79-4.65 (m, 1H), 2.83-2.53 (m, 2H), 2.18 (dtd, *J* = 11.2, 9.9, 5.3 Hz, 1H), 1.87 (dtd, *J* = 11.0, 10.3, 7.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 206.6, 133.6, 132.7, 131.7, 129.0, 128.4, 126.9, 126.3, 125.8, 125.0, 124.0, 86.9, 70.5, 39.3, 19.5; HRMS (ESI): calcd for $C_{15}H_{14}NaO_2$: 249,0891 $(M+Na)^+$, found: 249.0887.

2-(Thiophen-2-ylmethoxy)-cyclobutanone 3t. flash chromatography (90:10 hexanes/diethyl ether), 49 % yield (52 mg). FTIR (neat) ν: 2987, 2452, 1789, 1568, 1064 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ: 7.31 (dd, *J* = 5.1, 1.1 Hz, 1H), 7.06-7.03 (m,

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1H), 6.98 (dd, *J* = 5.0, 3.5 Hz, 1H), 4.91 (d, *J* = 12.4 Hz, 1H), 4.81 (d, *J* = 12.4 Hz, 1H), 4.75 (tt, *J* = 9.5, 2.1 Hz, 1H), 2.83-2.69 (m, 2H), 2.30 (dtd, *J* = 11.2, 10.0, 5.1 Hz, 1H), 1.99-1.89 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 206.4, 139.6, 127.3, 126.7, 126.4, 86.3, 66.3, 39.4, 19.6; HRMS (ESI): calcd for $C_9H_{10}NaO_2S$: 205.0299 $(M+Na)^+$, found: 205.0301.

General procedure for the synthesis of ketones 3w-z, 5a, 5x, 5y, 6-8. To a solution of alcohol (0.46 mmol) and 2-hydroxycyclobutanone **1a** (39.8 mg, 0.46 mmol) in CH_2Cl_2 (1 mL), *p*-toluenesulfonic acid (17 mg, 0.09 mmol) was added. The reaction mixture was stirred at 40 °C for 48 h and checked by GC-MS analysis until completion. The reaction solution was charged on a silica gel column and chromatographed (flash chromatography, hexanes/diethyl ether).

2-Phenethyloxy-cyclobutanone 3w. Flash chromatography, (90:10 hexanes/diethyl ether), 79 % yield (87 mg). FTIR (neat) v: 2990, 2889, 1790, 1553, 1160 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.33 (dd, *J* = 15.1, 13.8 Hz, 1H), 7.29-7.21 (m, 2H), 7.19 (dd, *J* = 12.5, 4.4 Hz, 2H), 4.64 (ddt, *J* = 20.8, 18.5, 7.1 Hz, 1H), 3.88 (dt, *J* = 9.3, 7.1 Hz, 1H), 3.72 (dt, *J* = 9.4, 7.4 Hz, 1H), 2.90 (t, *J* = 7.3 Hz, 2H), 2.82-2.58 (m, 2H), 2.36-2.21 (m, 1H), 1.89 (ddd, *J* = 21.2, 10.4, 7.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 206.5, 138.4, 128.9, 128.4, 126.3, 88.2, 71.1, 39.1, 36.3, 19.5; HRMS (ESI): calcd for $C_{12}H_{14}O_2$: 190,0994 $(M+Na)^+$, found: 213,0891.

2-(3-Phenyl-propoxy)-cyclobutanone 3x. flash chromatography (90:10 hexanes/diethyl ether), 80 % yield (95 mg). FTIR (neat) v: 2941, 2862, 1786, 1728, 1499, 1455, 1397, 1154, 1066, 1031, 741 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.31-7.21 (m, 2H), 7.18 (t, *J* = 7.4 Hz, 3H), 4.69-4.57 (m, 1H), 4.17-4.03 (m, 1H), 3.68 (dq, *J* = 9.2, 6.5 Hz, 1H), 3.53 (dt, *J* = 9.4, 6.5 Hz, 1H), 2.82-2.54 (m, 5H), 2.39-2.28 (m, 2H), 1.99-1.81 (m, 5H); ^{13}C NMR (126 MHz, CDCl3) δ: 206.6, 141.6, 128.3, 125.9, 125.8, 88.1, 69.5, 39.0, 32.0, 31.2, 19.4; HRMS (ESI): calcd for $C_{13}H_{16}O_2$: 204,1150 (M), found: 227,1050.

2-Allyloxy-cyclobutanone 3y. flash chromatography (90:10 hexanes/diethyl ether), 84 % yield (62 mg). FTIR (neat) v: 2927, 1732, 1277, 1120, 1069 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 5.85 (ddd, J = 16.1, 11.0, 5.8 Hz, 1H), 5.33-5.19 (m, 1H), 5.18-5.06 (m, 1H), 4.72-4.48 (m, 1H), 4.08 (ddd, *J* = 42.8, 12.6, 5.8 Hz, 1H), 2.81-2.62 (m, 2H), 2.29 (ddd, *J* = 20.6, 10.4, 4.9 Hz, 1H), 1.88 (ddd, *J* = 21.2, 10.4, 7.9 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 206.5, 133.9, 118.1, 87.1, 71.2, 65.4, 39.2, 29.0, 19.7; HRMS (ESI): calcd for $C_7H_{10}O_2$: 126,0681 $(M+Na)^+$, found: 149.0238.

2-Benzyloxy-cyclohexanone 5a. flash chromatography (90:10 hexanes/diethyl ether), 60 % yield (54 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.74-1.59 (m, 2H), 1.85-1.76 (m, 1H), 1.97-1.89 (m, 2H), 2.32-2.15 (m, 2H), 2.58-2.50 (m, 1H), 3.87 (ddd, *J* = 1.2, 5.5, 9.9 Hz, 1H), 4.47 (d, *J* = 12.1 Hz, 1H), 4.75 (d, *J* = 12.2 Hz, 1H), 7.32-7.26 (m, 1H), 7.38-7.33 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 23.0, 27.5, 34.6, 40.5, 71.6, 81.7, 127.7, 127.9, 128.4, 138.0, 210.2; The ^{1}H and ^{13}C NMR spectra were in agreement with the literature.[31]

2-Allyloxy-cyclohexanone 5x. flash chromatography (90:10 hexanes/diethyl ether), 71 % yield (48 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 1.31-1.25 (m, 4H), 1.74-1.67 (m, 2H), 2.44-1.95 (m, 2H), 4.09-3.98 (m, 1H), 4.35 (d, *J* = 7.2, 2H), 5.37-5.19 (m, 2H), 5.99-5.88 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 23.0, 27.6, 34.2, 40.5, 71.9, 83.0, 125.5, 135.8, 210.6; The ^{1}H and ^{13}C NMR spectra were in agreement with the literature.[32]

3-Benzyloxy-2-butanone 8. flash chromatography (90:10 hexanes/diethyl ether), 15 % yield (16 mg). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39-7.27 (m, 5H), 4.60 (d, *J* = 11.6, 1H), 4.48 (d, *J* = 11.6, 1H), 3.90 (m, 1H), 2.21 (s, 3H), 1.36 (d, *J* = 7.0, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 211.2, 137.7, 128.5, 128.0, 127.7, 80.9, 71.8, 25.0, 17.2. The ^{1}H and ^{13}C NMR spectra were in agreement with the literature.[33]

General procedure for the selective synthesis of substituted 2,7-dioxa-tricyclodecanes and dodecahydro-dioxins 4a,c,d,f,h,k,n,s,z 9, 10 using PTSA or AMB-15 as catalysts. To a solution of 2-hydroxycyclobutanone **1a** (0.58 mmol) and benzylic alcohol **2** (1.0 equiv.) in dry THF (5 mL), AMB-15® (0.2 g/mmol) was added. The reaction mixture was stirred at 65 °C for 4-12 hours and checked by GC-MS analysis until completion. The reaction solution was concentrated under reduced pressure and chromatographed on a silica gel column (flash chromatography, 95:5-90:10 hexanes/diethyl ether) affording the corresponding pure dimer.

1,6-Bis-benzyloxy-2,7-dioxa-tricyclo[6.2.0.03,6]decane 4a. Flash chromatography (95:5-90:10 hexanes/diethyl ether), 89 % yield (89 mg). FTIR (neat) v: 2928, 2874, 1604, 1509, 1455, 1332, 1225 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.37 (d, *J* = 7.1 Hz, 4H), 7.31 (t, *J* = 7.4 Hz, 4H), 7.26 (t, *J* = 3.5 Hz, 2H), 4.64 (d, *J* = 12.0 Hz, 2H), 4.45 (d, *J* = 12.0 Hz, 2H), 4.22-4.18 (m, 2H), 2.27 (td, *J* = 11.4, 3.9 Hz, 2H), 2.20-2.12 (m, 2H), 2.11-2.03 (m, 2H), 1.90 (tdd, *J* = 11.2, 8.5, 5.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 138.5, 128.2, 127.2, 127.2, 96.7, 70.3, 64.0, 29.0, 21.4; HRMS (ESI): calcd for $C_{22}H_{24}NaO_4$: 375,1572 $(M+Na)^+$, found: 375.1560.

1,6-Bis-benzyloxy-2,7-dioxa-tricyclo[6.2.0.03,6]decane 4c. flash chromatography (90:10 hexanes/diethyl ether), 40 % yield (44 mg). FTIR (neat) v: 2928, 1513, 1462, 1376, 1274, 1154, 806 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.42 (d, *J* = 6.3 Hz, 2H), 7.23-7.05 (m, 8H), 4.61 (d, *J* = 12.2 Hz, 1H), 4.41 (d, *J* = 12.2 Hz, 1H), 4.25-4.10 (m, 1H), 2.31 (s, 3H), 2.38-2.23 (m, 1H), 2.20-2.12 (m, 1H), 2.06 (dd, *J* = 20.7, 8.8 Hz, 1H), 1.95-1.86 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 136.4, 135.9, 129.8, 127.6, 127.3, 125.7, 96.7, 70.3, 62.3, 28.8, 21.5, 18.8; HRMS (ESI): calcd for $C_{24}H_{28}NaO_4$: 403.1885 $(M+Na)^+$, found: 403.1885.

1,6-Bis-benzyloxy-2,7-dioxa-tricyclo[6.2.0.03,6]decane 4d. flash chromatography (90:10 hexanes/diethyl ether), 88 % yield (97 mg). FTIR (neat) v: 2927, 1513, 1462, 1376, 1274, 1154, 806 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.30-7.21 (m, 3H),

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7.21-7.12 (m, 3H), 7.10 (d, *J* = 7.5 Hz, 2H), 5.24 (dd, *J* = 4.2, 1.8 Hz, 2H), 4.70 (d, *J* = 11.8 Hz, 2H), 4.46 (d, *J* = 11.8 Hz, 2H), 4.00-3.95 (m, 1H), 3.92 (td, *J* = 7.9, 5.8 Hz, 1H), 2.37 (s, 6H), 2.11-2.00 (m, 2H), 1.97 (ddd, *J* = 12.7, 7.2, 4.2 Hz, 4H), 1.86 (ddt, *J* = 10.9, 7.7, 5.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 138.1, 129.1, 128.6, 128.2, 125.4, 124.9, 103.1, 68.8, 66.9, 32.3, 23.4, 21.3; HRMS (ESI): calcd for $C_{24}H_{28}NaO_4$: 403.1885 $(M+Na)^+$, found: 403.1885.

1,6-Bis-benzyloxy-2,7-dioxa-tricyclo[6.2.0.03,6]decane 4f. flash chromatography (90:10 hexanes/diethyl ether), 42 % yield (88 mg). FTIR (neat) ν: 2997, 2345, 1532, 1201, 769 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.27 (d, *J* = 9.4 Hz, 8H), 4.58 (d, *J* = 12.2 Hz, 2H), 4.44-4.38 (m, 2H), 4.20-4.06 (m, 2H), 2.25 (td, *J* = 11.4, 3.9 Hz, 2H), 2.21-2.11 (m, 2H), 2.03 (dd, *J* = 20.5, 9.2 Hz, 2H), 1.94-1.84 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 136.9, 133.0, 128.5, 128.4, 96.7, 70.2, 63.3, 28.8, 21.4; HRMS (ESI): calcd for $C_{22}H_{22}Cl_2NaO_4$: 443,0793 (M), found: 443.0810.

1,6-Bis-benzyloxy-2,7-dioxa-tricyclo[6.2.0.03,6]decane 4h. flash chromatography (90:10 hexanes/diethyl ether), 71% yield (149 mg). FTIR (neat) ν: 2937, 2363, 1513, 1247, 1175, 1110, 1042 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.21 (t, *J* = 7.8 Hz, 1H), 6.96-6.91 (m, 2H), 6.79 (dd, *J* = 8.1, 2.3 Hz, 1H), 4.61 (d, *J* = 12.1 Hz, 1H), 4.43 (d, *J* = 12.1 Hz, 1H), 4.24-4.18 (m, 1H), 3.72 (s, 3H), 2.27 (td, *J* = 11.4, 3.8 Hz, 1H), 2.20-2.12 (m, 1H), 2.07 (dd, *J* = 21.0, 9.2 Hz, 1H), 1.90 (tdd, *J* = 11.1, 8.6, 5.6 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 136.4, 135.9, 129.8, 127.6, 127.3, 125.7, 96.7, 70.3, 62.3, 28.8, 21.5, 18.8; HRMS (ESI): calcd for $C_{24}H_{28}NaO_6$: 435,1784 $(M+Na)^+$, found: 435.1779.

1,6-Bis-benzyloxy-2,7-dioxa-tricyclo[6.2.0.03,6]decane 4k. flash chromatography (90:10 hexanes/diethyl ether), 92 % yield (224 mg). FTIR (neat) ν: 3002, 2984, 2307, 1612, 1515, 1330 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.57 (d, *J* = 8.1 Hz, 4H), 7.47 (d, *J* = 7.9 Hz, 4H), 4.68 (d, *J* = 12.7 Hz, 2H), 4.51 (d, *J* = 12.7 Hz, 2H), 4.17 (t, *J* = 6.5 Hz, 2H), 2.28 (td, *J* = 11.3, 3.6 Hz, 2H), 2.22-2.12 (m, 2H), 2.05 (dd, *J* = 19.8, 10.0 Hz, 2H), 1.91 (ddd, *J* = 19.6, 11.0, 5.7 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 142.5, 129.5 (q, *J* = 32.1 Hz), 127.1, 125.2, 96.8, 96.8, 70.2, 63.3, 28.7, 21.4; HRMS (ESI): calcd for $C_{24}H_{22}F_6NaO_4$: 511,1320 $(M+Na)^+$, found: 511.1379.

1,6-Bis-benzyloxy-2,7-dioxa-tricyclo[6.2.0.03,6]decane 4n. flash chromatography (90:10 hexanes/diethyl ether), 90 % yield (181 mg). Mp = 124-127° C; ATR (neat) ν: 3008, 2952, 2914, 2881, 2857, 2231, 1611, 1507, 1418, 1380, 1330 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 7.63 (dd, *J* = 13.8, 8.3 Hz, 4H), 7.52-7.38 (m, 4H), 4.67 (d, *J* = 13.3 Hz, 2H), 4.51 (d, *J* = 13.3 Hz, 2H), 4.22-4.02 (m, 2H), 2.33-2.21 (m, 1H), 2.21-2.09 (m, 2H), 2.09-1.97 (m, 2H), 1.95-1.83 (m, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 144.1, 132.1, 127.3, 118.7, 111.7, 96.7, 70.6, 63.5, 29.4, 21.4; HRMS (ESI): calcd for $C_{24}H_{22}N_2NaO_4$: 425,1471 $(M+Na)^+$, found: 425.14495.

1,6-Bis-benzyloxy-2,7-dioxa-tricyclo[6.2.0.03,6]decane 4s. flash chromatography (90:10 hexanes/diethyl ether), 51 % yield (115 mg). FTIR (neat) ν: 3002, 2920, 2821, 2708, 1711, 1588, 1475, 1260, 1079, 1035, 966 cm^{-1}; ^{1}H NMR (500 MHz, CDC_{l3}) δ: 8.04 (d, *J* = 8.4 Hz, 2H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.76 (d, *J* = 8.2 Hz, 2H), 7.57 (d, *J* = 7.0 Hz, 2H), 7.48-7.43 (m, 4H), 7.41 (dd, *J* = 8.3, 1.3 Hz, 2H), 7.35 (dd, *J* = 8.0, 7.2 Hz, 2H), 5.10 (d, *J* = 12.5 Hz, 2H), 4.89 (d, *J* = 12.4 Hz, 2H), 4.29 (t, *J* = 6.6 Hz, 2H), 2.34 (td, *J* = 11.3, 3.4 Hz, 2H), 2.23-2.15 (m, 2H), 2.12 (dt, *J* = 18.8, 6.6 Hz, 2H), 2.03-1.82 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 134.0, 133.5, 131.3, 128.4, 127.9, 126.0, 125.5, 125.3, 125.2, 123.7, 107.3, 96.9, 70.5, 62.4, 28.9, 21.6; HRMS (ESI): calcd for $C_{30}H_{28}NaO_4$: 475,1885 $(M+Na)^+$, found: 475.1872.

1,6-Bis-propynoxy-2,7-dioxa-tricyclo[6.2.0.03,6]decane 4z. flash chromatography (90:10 hexanes/diethyl ether), 84 % yield (104 mg). FTIR (neat) ν: 2958, 2868, 2360, 2121, 1438, 1284, 1229, 1175, 1120, 1052, 659 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ: 4.17 (td, *J* = 6.7, 2.9 Hz, 2H), 4.14 (d, *J* = 2.5 Hz, 4H), 2.39 (t, *J* = 2.4 Hz, 2H), 2.29-2.20 (m, 2H), 2.21-2.12 (m, 4H), 1.92-1.80 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ: 97.2, 80.3, 73.7, 70.0, 50.5, 28.9, 21.2; HRMS (ESI): calcd for $C_{14}H_{16}NaO_4$: 271.0946 $(M+Na)^+$, found: 271.0942.

1,6-Bis-benzylthio-2,7-dioxa-tricyclo[6.2.0.03,6]decane 9. flash chromatography (90:10 hexanes/diethyl ether), 68 % yield (130 mg). FTIR (neat) ν: 2937, 2356, 1802, 1396, 1140, 1068, 771 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (t, *J* = 7.3 Hz, 4H), 7.31 (dd, *J* = 13.9, 7.2 Hz, 4H), 7.24 (dd, *J* = 13.3, 7.2 Hz, 2H), 4.10 (q, *J* = 7.9 Hz, 2H), 3.91 (dd, *J* = 17.9, 12.9 Hz, 4H), 3.83 (t, *J* = 11.8 Hz, 4H), 2.40-2.23 (m, 2H), 2.10-1.93 (m, 4H), 1.93-1.72 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ: 138.5, 138.0, 129.2, 129.1, 128.6, 128.5, 127.1, 127.0, 76.0, 67.5, 34.9, 34.3, 29.5, 29.3; HRMS (ESI): calcd for $C_{22}H_{24}NaO_2S_2$: 407,1115 $(M+Na)^+$, found: 407,1117.

10. flash chromatography (90:10 hexanes/diethyl ether), 41 % yield (37 mg). FTIR (neat) ν: 2988, 1217, 1060 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39-7.19 (m, 10H), 4.63 (q, *J* = 3.5 Hz, 2H), 4.52 (d, *J* = 12.0 Hz, 2H), 3.60 (dd, *J* = 11.5, 4.7 Hz, 2H), 2.29 (d, *J* = 14.2 Hz, 2H), 2.21-2.03 (m, 2H), 1.98-1.87 (m, 2H), 1.86-1.74 (m, 4H), 1.73-1.45 (m, 2H), 1.40-1.31 (m, 2H), 1.31-1.20 (m, 2H), 0.85 (dd, *J* = 10.3, 7.0 Hz, 2H).; ^{13}C NMR (101 MHz, $CDCl_3$) δ: 139.3, 130.9, 128.1, 127.2, 127.0, 96.0, 30.8, 27.8, 25.9, 25.8, 23.9, 22.8, 22.1; HRMS (ESI): calcd for $C_{26}H_{32}NaO_4$: 431,2198 $(M+Na)^+$, found: 431,2193.

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***In thid document you will find attached The Chem-Draw copies of the schemes and figures for the submited manuscript**

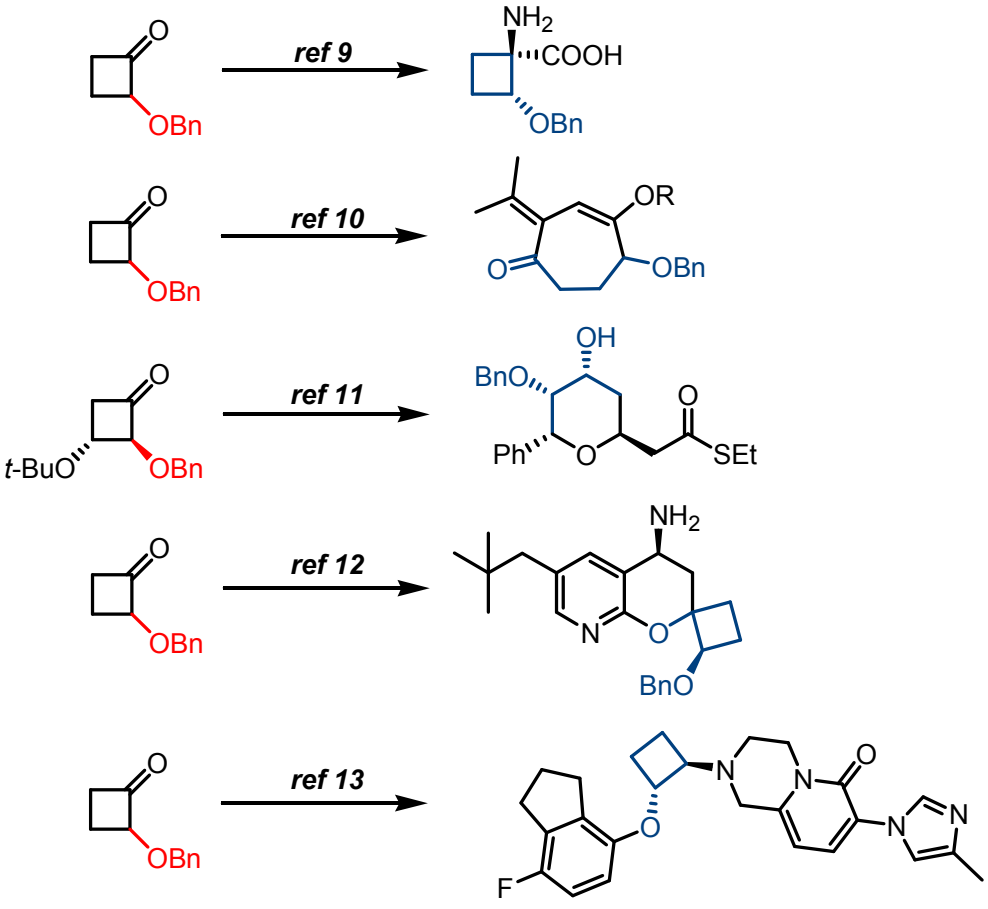

Figure 1

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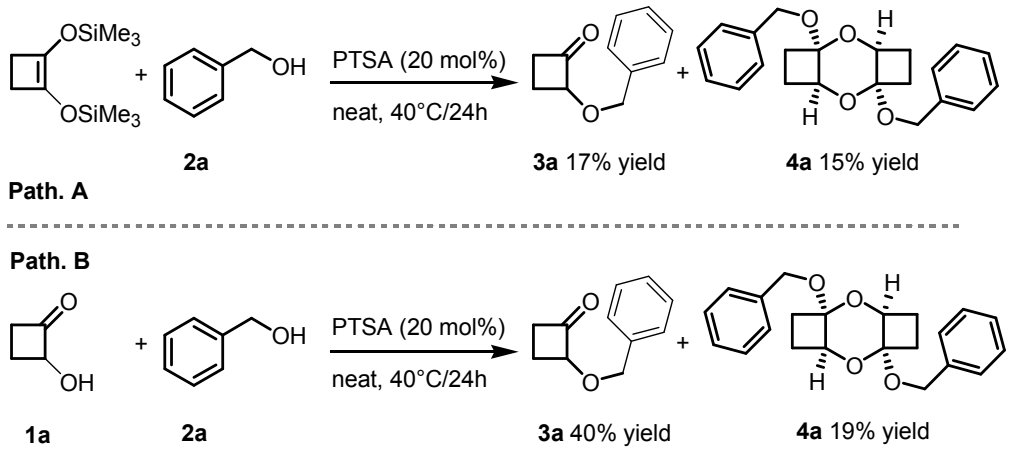

Scheme 1

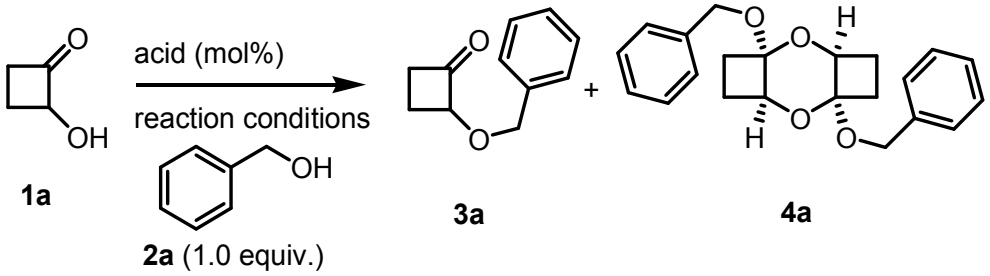

Table 1

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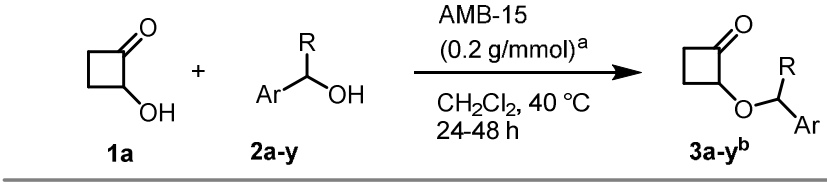

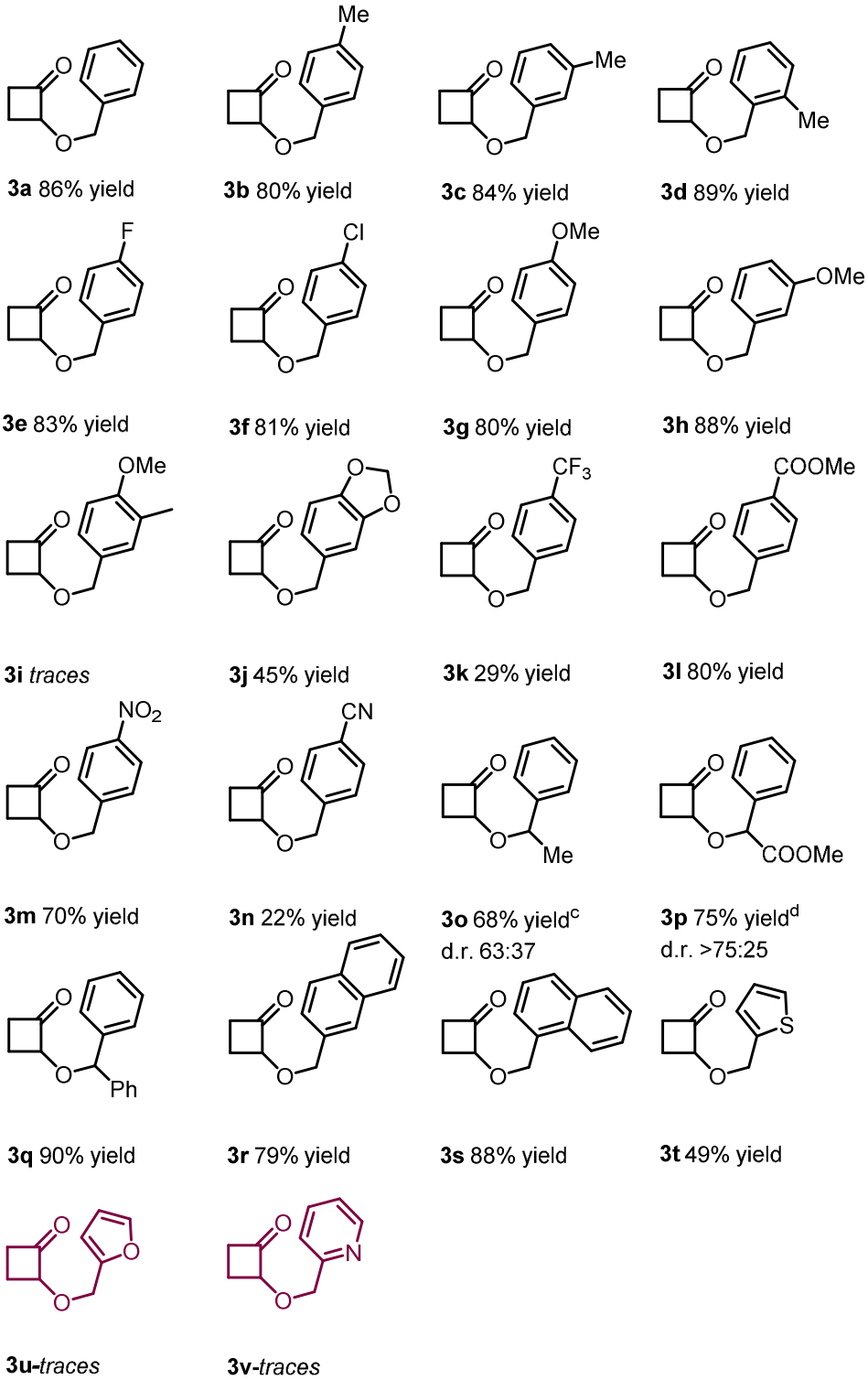

Scheme 2

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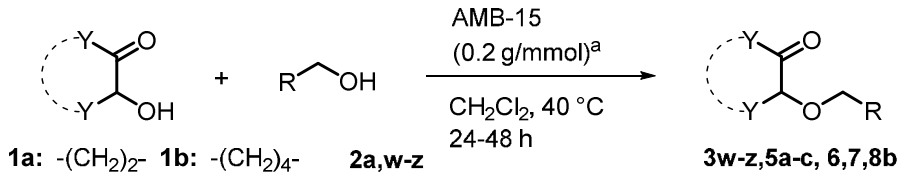
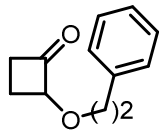


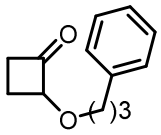
1a: $-(CH_2)_2-$ **1b:** $-(CH_2)_4-$
1c: Y = X = Ph **1d:** $-C_6H_4-$
1e: Y = X = Me

2a,w-z

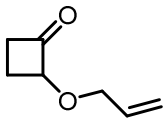
3w-z,5a-c, 6,7,8b



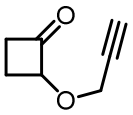
3w 79% yield



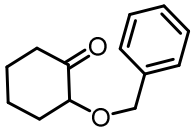
3x 80% yield



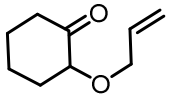
3y 84% yield



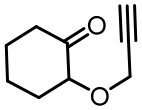
3z traces



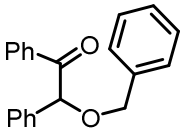
5a 80% yield



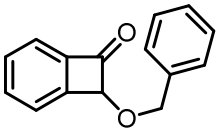
5x 71% yield



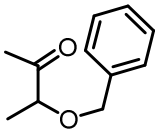
5y 68% yield



6 0% yield



7 0% yield



8 15% yield

Scheme 3

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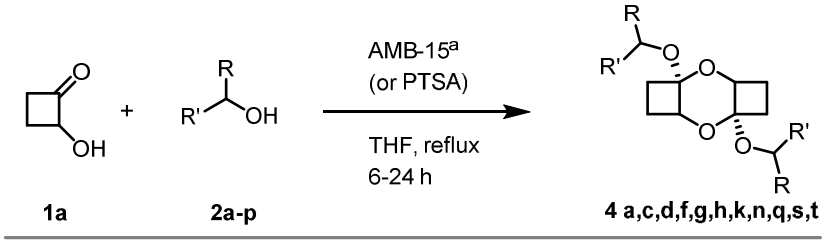
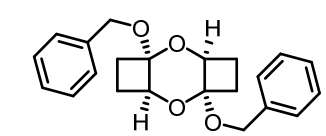
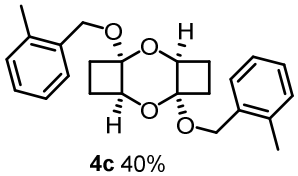
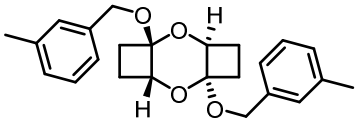




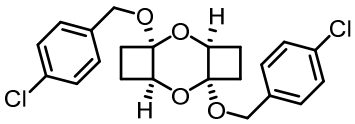
4a 89% (PTSA)
87% (AMB-15)



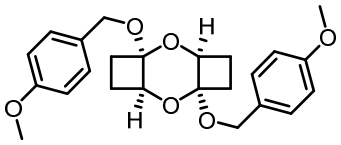
4c 40%



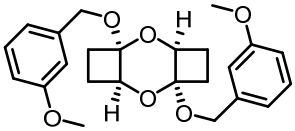
4d 88%



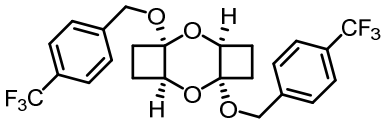
4f 42%



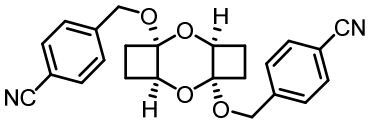
4g 0%



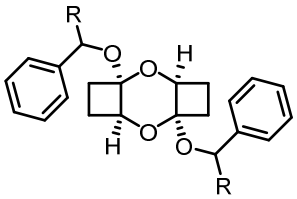
4h 71%



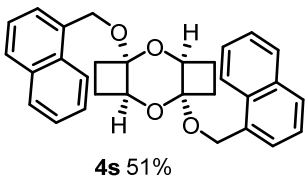
4k 92%



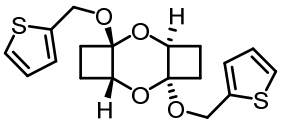
4n 90%
(8:1cis/trans)



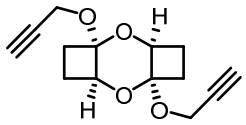
4p, R = COOMe 0%
4q, R = Ph 0%



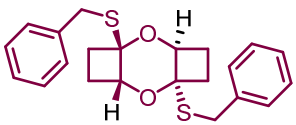
4s 51%



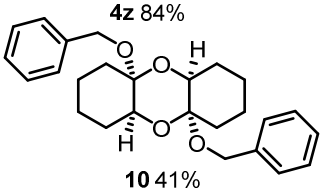
4t 69%



4z 84%



9 68%



10 41%

Scheme 4

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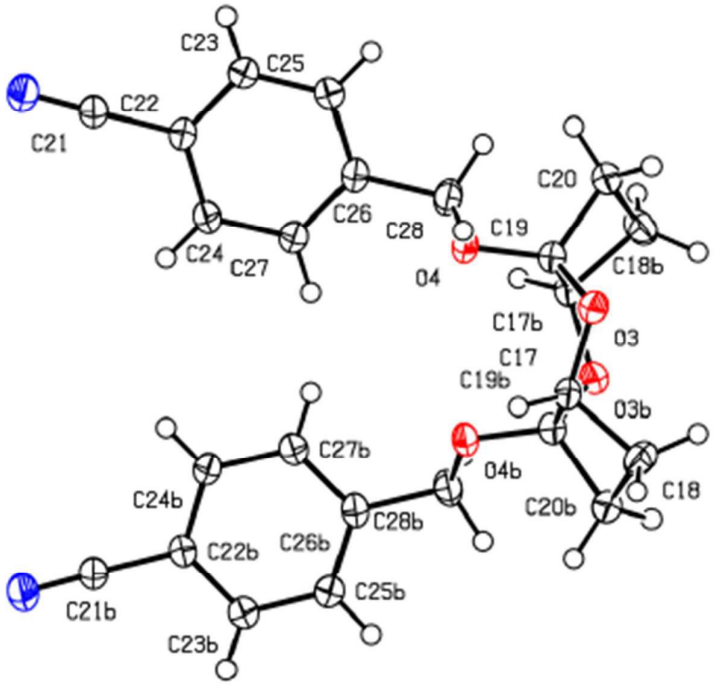

Figure 2

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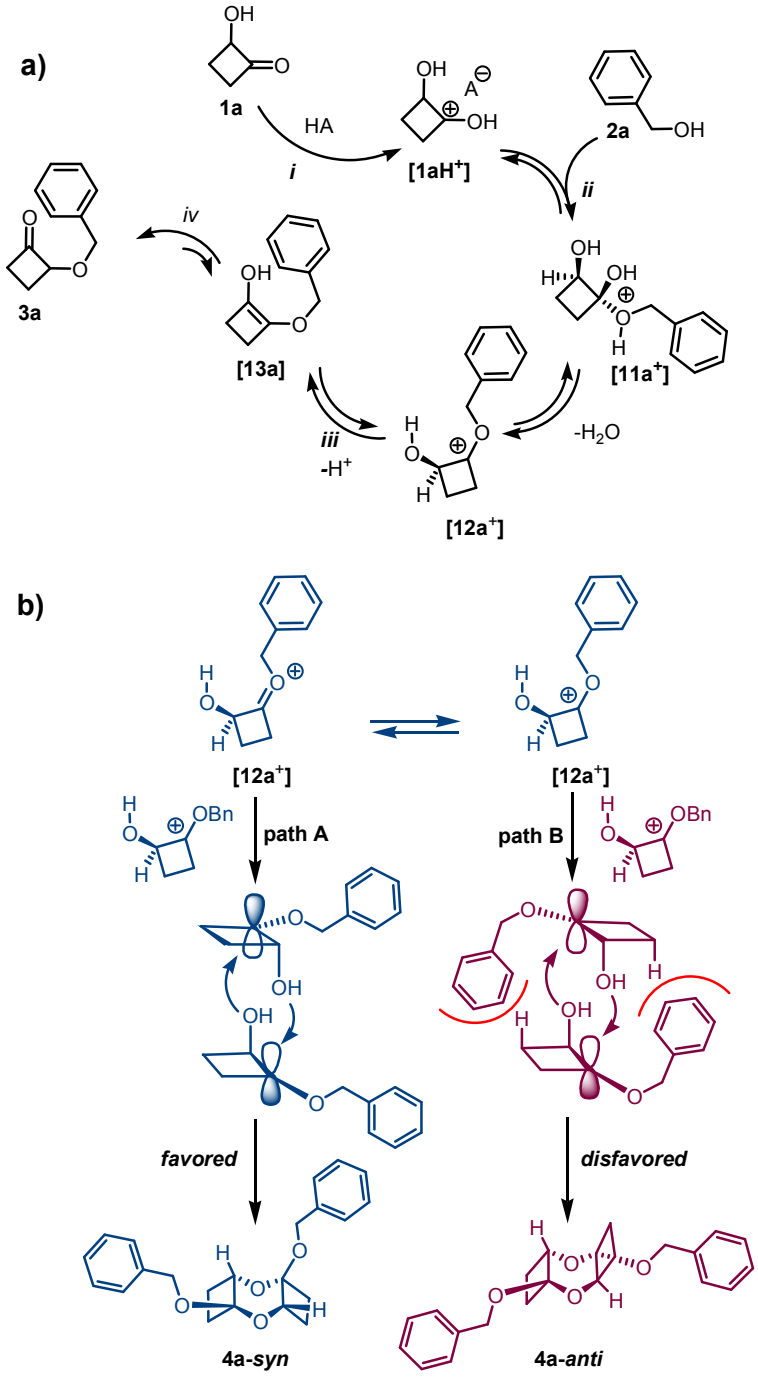

Scheme 5

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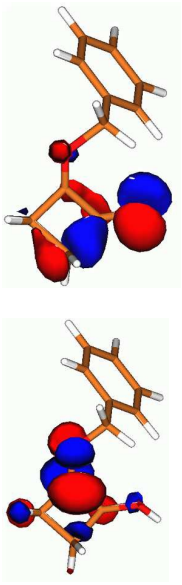

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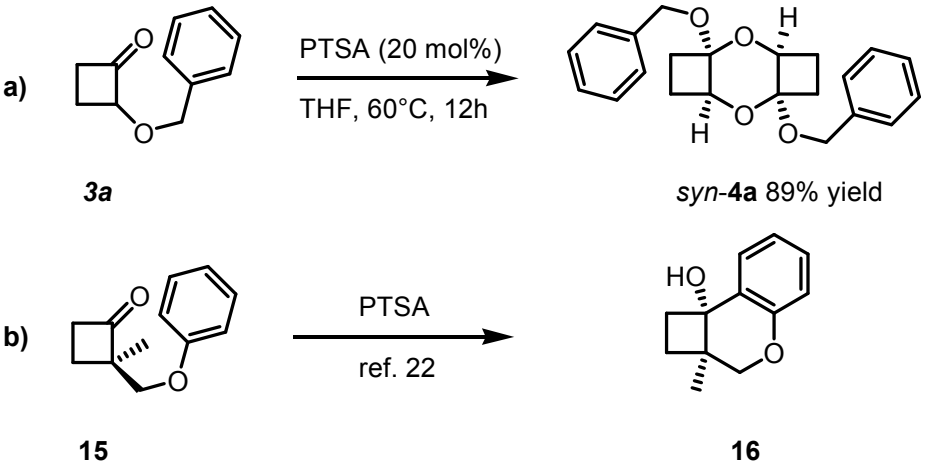
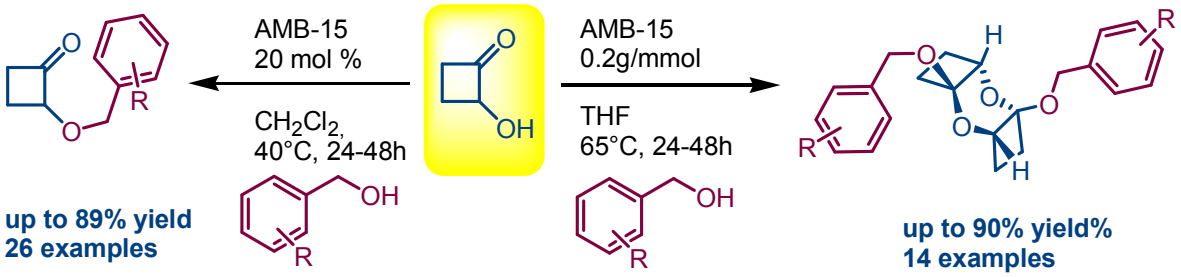


Scheme 6



Graphical abstract