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An Unexpected Michael–Aldol–Smiles Rearrangement Sequence for the Synthesis of Versatile Optically Active Bicyclic Structures by Using Asymmetric Organocatalysis

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Abstract: A facile and simple organocatalytic procedure to generate optically active 6-alkyl- and 6-aryl-substituted bicyclo[2.2.2]oct-5-en-2-ones is presented. The reaction is catalysed by a 9-amino-9-deoxyepiquinine trifluoroacetic acid salt, which activates α,β-unsaturated cyclic ketones for the 1,4-addition of β-keto benzothiazoyl sulfones in a stereoselective fashion. Subsequent intramolecular aldol reaction and Smiles rearrangement gives rise to important optically active bicycles, which are a common motif in natural products, ligands in asymmetric catalysis and substrates for Cope rearrangements, photochemical reactions, radical cyclisations and metathesis. Different bicyclic structures were obtained by utilisation of various cyclic enones or by performing ring-expanding reactions. Furthermore, two possible mechanistic pathways are outlined and discussed.

Keywords: asymmetric catalysis · bicycles · enones · organocatalysis · Smiles rearrangement

Introduction

The application of substituted bicyclo[2.2.2]oct-5-en-2-ones in organic synthesis has been plentiful (Figure 1). Besides their use as substrates in various photochemical reactions,[1] for example, in di-π-methane or oxa-di-π-methane rearrangements and photoinduced electron-transfer reactions, they are suitable precursors for the examination of radical cyclisation reactions, leading to the formation of the unique tricyclo[4.3.1.0^{3,7}]decane framework, which is present in the pupukeanane class of natural products.[2] On the other hand, these bicyclic structures have also found application as key intermediates in the synthesis of chiral bicyclo[2.2.2]dienes, serving as effective ligands for asymmetric rhodium-catalysed 1,4-additions as described by the groups of Carreira and Hayashi.[3] Besides the presence of the bicyclo[2.2.2]oct-5-en-2-one motif in natural products, such as obtunone and chamaecypanone,[4] it has also been shown that the elaboration of the bicyclic core in anionic oxy-Cope rearrangements gives rise to functionalised decalin systems, which are contained in a variety of terpenoids and steroids.[5]

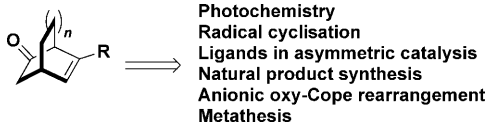

Figure 1. Important applications of substituted bicyclo[2.2.2]oct-5-en-2-ones.

Thus far, synthetic approaches to this important class of compounds have been almost exclusively limited to Diels–Alder reactions between an electron-deficient alkene and masked *o*-benzoquinones, or other 2,4-cyclohexadienone substitutes.[6] High reaction temperatures and limited substitution patterns are some of the drawbacks of this synthetic approach. Murakami and Ashida reported the synthesis of benzobicyclo[2.2.2]octenones by a nickel-catalysed alkene insertion,[7] whereas the strategy of Srikrishna et al. relied on an intramolecular alkylation, starting from carvone and therefore giving access to chiral bicyclic structures.[8] More recently, a racemic approach involving intermolecular Michael addition followed by intramolecular aldol condensation has been described.[9] Upon treatment with trifluoromethanesulfonic acid and phosphorus pentoxide, the corresponding racemic bicyclo[2.2.2]oct-5-en-2-ones were obtained in good yields, although the highest yields were ob-

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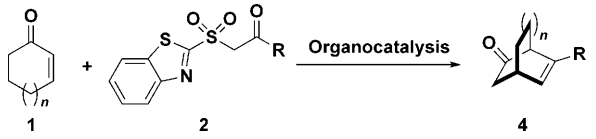
tained under additional microwave irradiation of the reaction mixture.

Nowadays, organocatalysis has emerged as a powerful tool for the introduction of chirality into a substrate,[10] and the investigations of asymmetric organocatalytic processes during the last few years included also Diels–Alder reactions. In this context isoquinuclidines or amino-, hydroxyl- and nitro-substituted bicyclo[2.2.2]octanones have been synthesised by cycloaddition of activated cyclohexenone derivatives with imines, enolisable aldehydes or nitroolefins, respectively.[11] Tan and Soh have utilised 3-hydroxy-2-pyridones as dienes in an organocatalytic fashion, giving access to azabicyclo[2.2.2]octenone frameworks,[11] whereas a tandem strategy to build up bicyclo[3.3.1]nonanes has been recently published by Tang and co-workers.[11m]

Despite the achievements published for the synthesis of bicyclo[2.2.2]oct-5-en-2-one motifs, there is still need for a general asymmetric approach. Herein, we present the asymmetric organocatalytic synthesis of 6-alkyl- and 6-aryl-substituted bicyclo[2.2.2]oct-5-en-2-ones **4** in good yields and with high enantioselectivities. The key step of this procedure is based on the organocatalysed Michael reaction of cyclic enones **1** with a β-keto benzothiazoyl (BT) sulfone **2**, catalysed by 9-amino-9-deoxyepiquinine trifluoroacetic acid salt **3**[12] (Scheme 1). The resulting addition product can be utilised to build up the bicyclic core under mild conditions, by an aldol reaction–Smiles rearrangement sequence. Depending on the applied conditions, two possible mechanistic pathways can be considered, which also will be discussed herein.

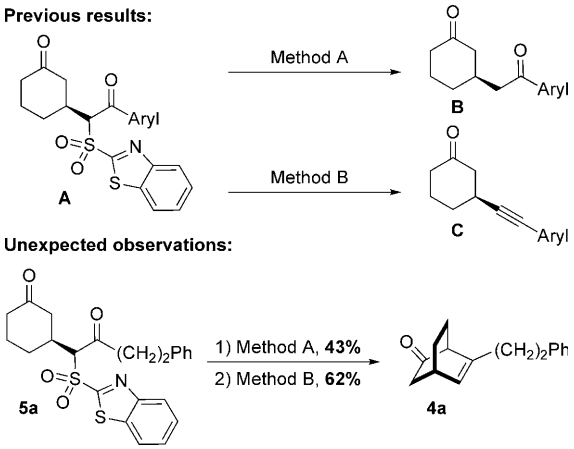


Scheme 1. Organocatalytic synthesis of 6-alkyl- and 6-aryl-substituted bicyclo[2.2.2]oct-5-en-2-ones.

Results and Discussion

In earlier work,[13] we have demonstrated that aryl-substituted Michael adducts **A** can be readily converted into desulfonylated products **B**, or alkynylated products **C**, selectively, depending on the applied reaction conditions (Scheme 2, top).[13a] During these studies, we obtained unexpected results for the transformation of the alkyl-substituted adduct **5a** (Scheme 2, bottom).

Upon treatment of **5a** with solid Na_2CO_3 in a THF/*i*PrOH mixture (method A, a procedure applied for removal of the sulfone unit), or protection of the ketone group, followed by treatment with an aqueous solution of Na_2CO_3 in the presence of tetrabutylammonium iodide (TBAI) as a phase-transfer catalyst, (method B, conditions used for synthesising β-alkynylated ketones), the same product **4a** was obtained in 43 and 62% yield, respectively. By 2D NMR analysis, the

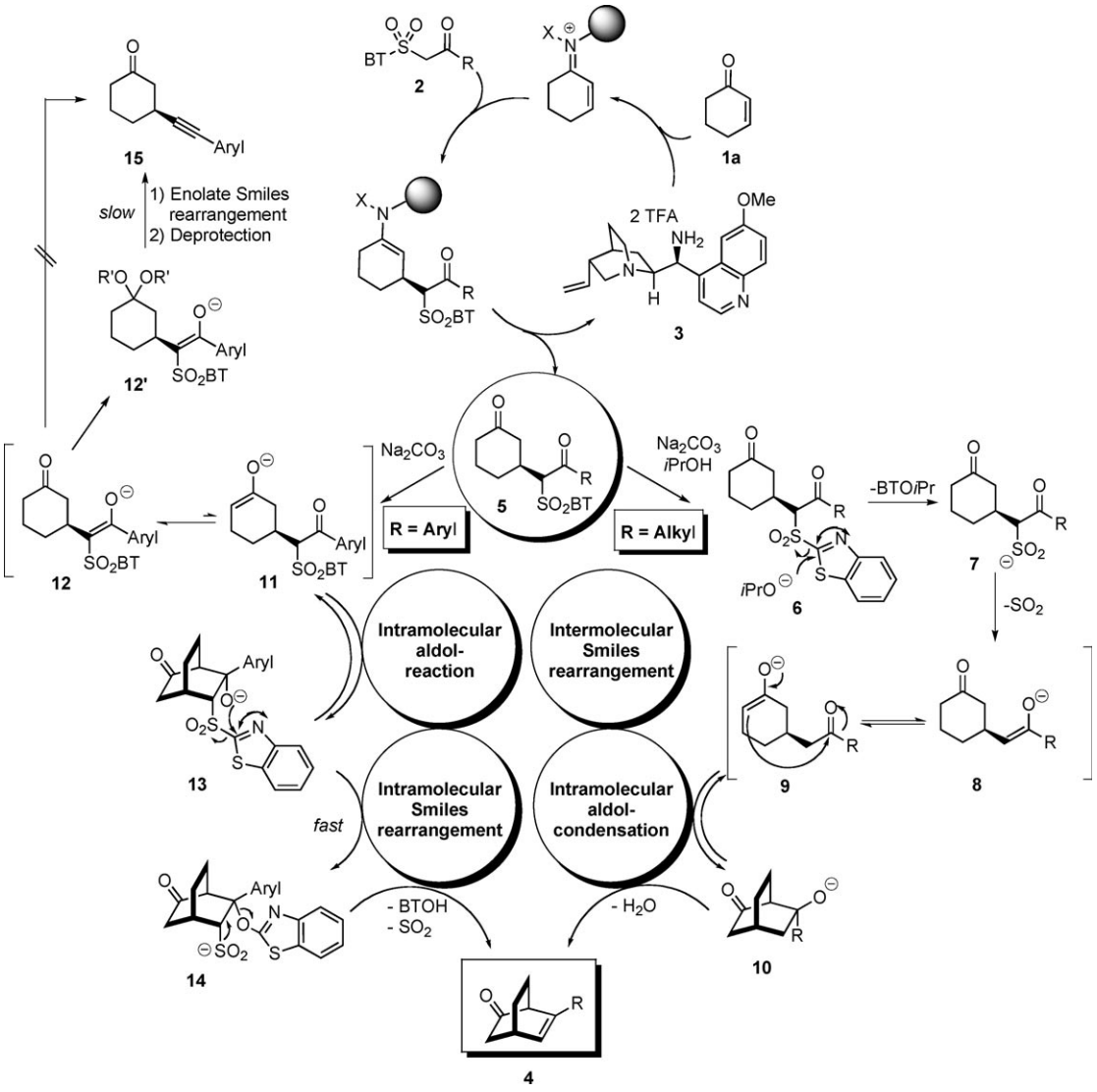


Scheme 2. Unexpected cyclisation reaction of alkyl-substituted Michael adduct **5a**. method A: Na_2CO_3, THF, *i*PrOH, 45 °C; method B: 1) 2-ethyl-2-methyl-1,3-dioxolane, toluene sulfonic acid (*p*TSA), 2) saturated aqueous solution of Na_2CO_3, tetrabutylammonium iodide (TBAI), toluene, 45 °C, 3) 50% aq. trifluoroacetic acid (TFA).

product was identified as the bicyclic structure **4a**, which, to our delight, was formed with 90% enantiomeric excess (*ee*).

Due to the high enantiomeric excess generated in these reactions, and the importance of bicyclo[2.2.2]oct-5-en-2-ones in synthetic chemistry, we were interested in elucidating a plausible mechanism to explain the reaction course of adduct **5a** towards the bicyclic product **4a** (Scheme 2). A possible mechanism is outlined in Scheme 3, right. Starting from the 1,4-addition intermediate **5**, which was obtained in a stereoselective manner in the organocatalytic cycle,[14] it is assumed that the presence of Na_2CO_3 and a protic solvent, such as *i*PrOH, results in the generation of small amounts of the isopropoxide anion (method A). It is proposed that the alkoxide performs a nucleophilic attack at the C=N carbon atom of the heterocyclic ring in **6**. Subsequent cleavage of benzotriazolyl-O*i*Pr (BT-O*i*Pr) gives **7**, and release of SO_2 leads to the formation of the enolate anion **8**. This removal of the sulfone moiety can be considered as an intermolecular Smiles rearrangement.[15] Due to the presence of two ketone functionalities, the equilibrium of the enolate species **8** and **9** seems to be dependent on the nature of the R substituent in the β-keto benzothiazoylsulfone. An aryl group stabilises intermediate **8**, thus making it possible to stop the reaction at the 1,5-dicarbonyl compound,[13a] whereas an aliphatic R substituent will favour intermediate **9**. An intramolecular aldol reaction provides bicyclic structure **10** and subsequent condensation finally results in the 6-alkyl-substituted bicyclo[2.2.2]oct-5-en-2-one **4**. To facilitate the cyclisation for intermediate **9** with R = aryl, harsher conditions are believed to be required in analogy with the report of Jung and Maderna,[9] using strongly acidic conditions in combination with microwave irradiation.

To expand the scope of the reaction to alkyl and aryl substituents, a thorough screening of bases, solvents and additives was performed using cyclohexenone **1a** and the alkyl-substituted sulfone **2a** as model substrates. The results are presented in Table 1. Although this process is a clean reac-



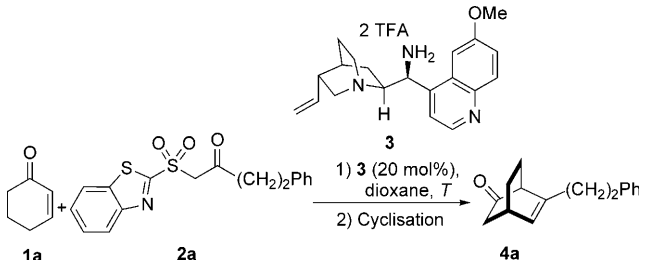
Scheme 3. Mechanistic aspects of the cyclisation reaction.

tion, under the initial reaction conditions, prolonged reaction times were required. After 24 h at 45 °C, only 17 % conversion was achieved, and full conversion was only obtained after three days (Table 1, entries 1 and 2). The use of MeOH instead of *i*PrOH led to an increase in conversion after 24 h (Table 1, entry 3). The reaction rate could be improved by the use of stronger bases such as Cs_2CO_3 or NaOMe (Table 1, entries 4 and 5). Full conversion was obtained after 24 and 2 h, respectively, although the occurrence of side reactions resulted in low yields of **4a**.

The base dependence on the reaction outcome led us to investigate different reaction conditions (method B, Scheme 2), in which a saturated aqueous solution of Na_2CO_3 in combination with a phase-transfer catalyst was employed. Previously, these conditions were shown to favour the enolate Smiles rearrangement, leading to the formation of an alkyne group in the ketal-protected Michael adducts (see Scheme 2, middle).[13a] However, this alkyne formation was only possible when using adduct **5**, carrying R = aryl in the sulfone moiety. For the aliphatic substrates, the bicyclic compound **4** was formed exclusively, independent of the presence of the ketal protecting group. This was demonstrated by subjecting the adduct **5a** directly to the basic/phase-transfer conditions (no ketal protection). After 24 h, we obtained full conversion and **4a** was formed in 58 % yield with 95 % *ee* (Table 1, entry 6). Access to *ent*-**4a** could be achieved by changing the catalyst employed (Table 1, entry 7). As the organocatalytic Michael addition of aliphatic-substituted BT-sulfones normally results in prolonged reaction times (48 h), we tried to perform this step at 45 °C (Table 1, entry 8). Although full conversion was achieved after 28 h, the enantiomeric excess of the product decreased to 92 % *ee*. The two-step sequence can also be performed in a one-pot procedure without affecting the enantioselectivity; however, the isolated yield was slightly lower (42 %, 94 % *ee*).

With the optimised reaction conditions in hand, we turned our attention to the application of this method to dif-

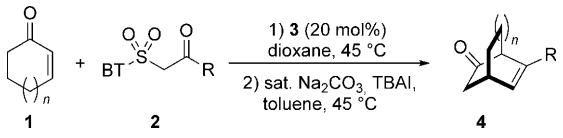
Table 1. Optimisation of the organocatalytic 1,4-addition of cyclohexenone **1a** with BT-sulfone **2a**, followed by cyclisation to bicycle **4a**.[a]

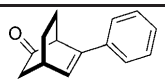
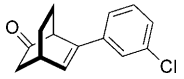
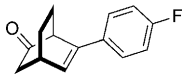
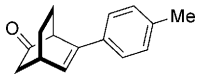
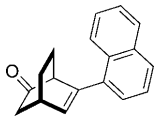
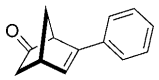
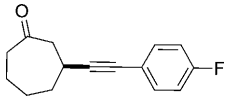


Entry	*T* [°C]	Cyclisation conditions	Conv. [%][b]	Yield [%][c]	*ee* [%][d]
1	RT	Na_2CO_3, THF/*i*PrOH, 45 °C, 24 h	17	–	nd
2	RT	Na_2CO_3, THF/*i*PrOH, 45 °C, 3 d	100	43	90
3	RT	Na_2CO_3, THF/MeOH, 45 °C, 24 h	31	–	nd
4	RT	Cs_2CO_3, THF/*i*PrOH, 45 °C, 24 h	100	25	nd
5	RT	NaOMe, THF/*i*PrOH, 45 °C, 2 h	100	16	nd
6	RT	sat. Na_2CO_3, TBAI, toluene, 45 °C, 24 h	100	58	95
7[e]	RT	sat. Na_2CO_3, TBAI, toluene, 45 °C, 24 h	100	60	−94
8	45	sat. Na_2CO_3, TBAI, toluene, 45 °C, 24 h	100	54	92

[a] Experimental conditions: enone **1a** (1.0 mmol, 2 equiv) was added to a stirred solution of **2a** (0.5 mmol, 1 equiv) and catalyst **3** (20 mol%) in dioxane (5 mL) at the indicated temperature. Then a solution of **5** (0.5 mmol) in a 1:1 mixture toluene/saturated aqueous solution of Na_2CO_3 (10 mL) was treated with TBAI (1.2 equiv) and stirred at 45 °C. [b] Determined by NMR spectroscopy. [c] Isolated yields. [d] Determined by chiral stationary phase HPLC. [e] The quasi-enantiomer of **3** was used.

Table 2. Scope of the organocatalytic 1,4-addition of enones **1** with BT-sulfones **2**, followed by cyclisation to the bicycles **4**.[a]



Entry	Product	Yield [%][b]	*ee* [%][c]
1		**4b** 51	91
2		**4c** 49	95
3		**4d** 44	94
4		**4e** 50	94
5		**4f** 59	97
6		**4g** 44	60
7[d]		**4h** 51	98

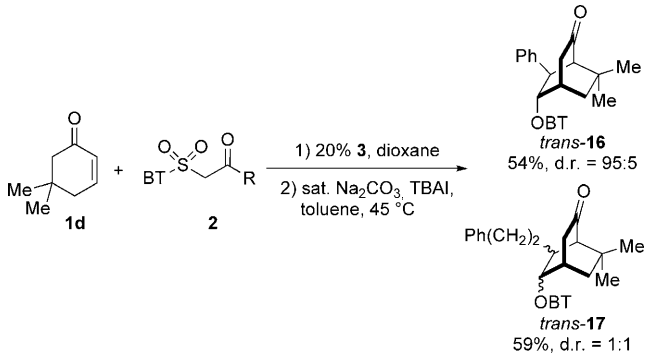
[a] Experimental conditions: enone **1** (1.0 mmol, 2 equiv) was added to a stirred solution of **2** (0.5 mmol, 1 equiv) and catalyst **3** (20 mol%) in dioxane (5 mL). Then, a solution of **5** (0.5 mmol) in a 1:1 toluene/saturated aqueous solution of Na_2CO_3 (10 mL) was treated with TBAI (1.2 equiv) and stirred at 45 °C. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC. [d] Reaction was performed at 65 °C.

ferent aromatic BT nucleophiles **2** (Table 2). As previously stated, aryl-substituted nucleophiles did not undergo cyclisation when using sodium carbonate (method A, Scheme 2). Having developed a more reactive process for obtaining the bicyclic structures **4**, we decided to apply these conditions to the aryl-substituted sulfones. The phenyl-substituted sulfone **2b** was selected and employed under these new conditions. To our delight, full conversion of the cyclisation process was obtained after 24 h. The 6-phenyl-substituted bicyclo[2.2.2]oct-5-en-2-one **4b** was isolated in 51% yield and with a high enantioselectivity of 91% *ee* (Table 2, entry 1). Apparently, by omitting ketal protection, alkyne formation was completely suppressed, thus favouring the formation of the 6-aryl-substituted bicyclic compounds **4** (compare conditions in Scheme 2, middle, with Table 2).

With these results in hand, the scope of this reaction is not exclusively limited to the synthesis of 6-alkyl-substituted bicyclo[2.2.2]oct-5-en-2-ones. A range of aromatic BT-sulfones was applied and the corresponding bicycles were isolated in moderate yields (Table 2, entries 2–4); however, no byproducts were detected. The nature and position of the substituent attached to the aromatic ring have no influence on the high enantioselectivities obtained (94–95% *ee*). An increase of the steric bulk appears to be favourable, since the 2-naphthyl substituent gave the highest yield and enantioselectivity (59%, 97% *ee*, Table 2, entry 5).

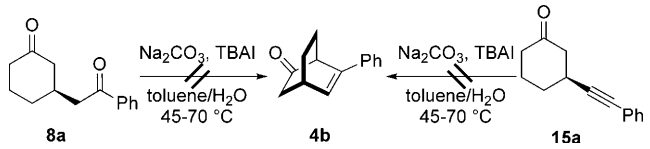
Extension of this concept for the synthesis of bicyclo[2.2.1]heptenone **4g** was also achieved (Table 2, entry 6). However, the modest enantioselectivity of 60% *ee* was consistent with previously reported results for reactions of cyclopentenones.[16] Unfortunately, the synthesis of bicyclo[3.2.2]nonenones failed and only the alkynylated ketone **4h** was isolated, although in good yield and with a very high *ee* value (98% *ee*) (Table 2, entry 7). It should be pointed out that in Table 2, entries 1–6, no alkyne products were observed.

Moreover, the application of this protocol to 5,5-dimethyl-cyclohex-2-en-1-one **1d** was also carried out (Scheme 4). However, the bicyclic structures obtained were not consistent with the expected results. By MS and NMR spectroscopy analysis, the products were identified as the diastereoisomers *trans*-**16** and *trans*-**17**, respectively. The formation of these products can be rationalised by an additional attack of BT-OH on the double bond. Surprisingly, depending on the applied BT-sulfone, the corresponding *trans*-configured diastereoisomers were formed with different selectivities. Whereas R = Ph results in the formation of *trans*-**16** with high diastereoselectivity (95:5 diastereomeric ratio (d.r.)), when R = alkyl, a 1:1 mixture of the two diastereomers *trans*-**17** was obtained.



Scheme 4. Unexpected side reaction when 5,5-dimethyl cyclohexenone **1d** was employed.

To obtain further insight into the mechanism for the formation of the cyclic compounds with aromatic substituents, a series of experiments was carried out. Attempts to transform the pre-isolated aryl-substituted 1,5-diketone product **8a** into its bicyclic counterpart **4b** under the optimised reaction conditions was unsuccessful (Scheme 5, left). This observation led us to believe that the presence of an intact BT-sulfone group is crucial for the cyclisation of aryl-substituted Michael adducts **5**, hence it is less likely that the reaction proceeds through a 1,5-diketone intermediate.



Scheme 5. Unsuccessful cyclisation reactions with isolated diketone **8a** and alkynylated ketone **15a**.

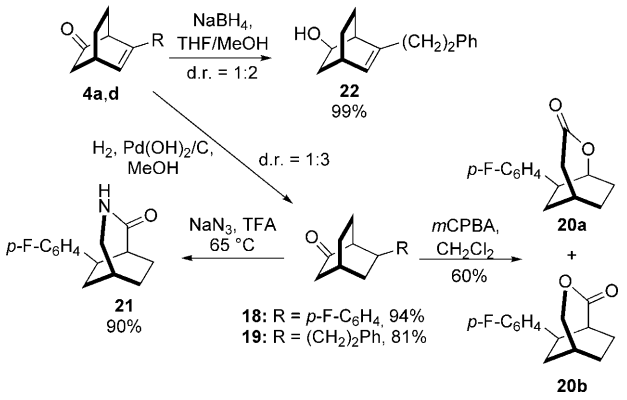
The results prompted us to propose an alternative mechanism for R = aryl, as presented in Scheme 3, left pathway. When adduct **5** is subjected to Na_2CO_3 under phase-transfer conditions, an equilibrium between enolates **11** and **12** favours **12**. However, subsequent intramolecular aldol reaction of **11** through nucleophilic attack of the cyclic enolate anion takes place, giving the bicycle **13**. Intermediate **13** undergoes a Smiles rearrangement to give **14**, followed by the formation of bicyclo[2.2.2]octenone **4**, BT-OH and SO_2. Because all reaction steps prior to the Smiles rearrangement are reversible, the outcome of the reaction course is believed to be greatly influenced by the reaction rate of the final step. Despite only small amounts of the unfavourable, but reactive enolate **11** being present, the last irreversible reactions from intermediate **13** to **4** are fast. It has been observed that the transformation of **13** to **4** is completed within hours, whereas the formation of the triple bond (**12** to **15**) requires days. The preference for the bicyclic compound **4** is driven by a faster intramolecular Smiles rearrangement of **13** to **14**, compared with the enolate Smiles rearrangement of **12** to **15**. Furthermore, to rule out the possibility of conversion from alkynylated products **15** to bicycles **4** (suggesting a pathway from the favourable enolate **12** through alkyne product **15** to final product **4**), isolated **15a** was subjected to the basic reaction conditions. This reaction did not result in any formation of bicycle **4b** (Scheme 5, right), which supports the proposed alternative mechanism (through the enolate **11**) for the formation of the bicycles **4** when R = aryl.

It has previously been stated that under the present reaction conditions, the ketal-protected adducts (R = aryl) give the alkyne product **15** (Scheme 2, middle) This is rationalised by the fact that when the ketone functionality is protected, the acidity of the α-methylene protons is lowered to the extent that the enolate **11** is not present. Therefore, the transformation to the alkynylated product **15** becomes the faster process, although small traces of the bicyclic compound could be observed in the crude product mixture.

On the contrary, when R = alkyl, reasonable doubts can be raised as to whether the aldol cyclisation takes place prior to or after the desulfonylation step (Scheme 3, pathway on the right vs. pathway on the left). An indication favouring the presence of a diketone intermediate (**9**) is that even when the ketone motif is protected as a ketal and when employing milder reaction conditions, the bicycle is always formed as the sole product. As stated, masking the ketone moiety raises the pK_a of the α-methylene protons significantly. Formation of a reactive anion in the presence of the doubly activated methylene adjacent to the sulfone seems unlikely. In the pathway on the right (Scheme 3), although one activation group (sulfonyl) is removed, the acidity of the α-carbon atom of the ketal group is apparently high enough to undergo intramolecular aldol reaction.

To summarise, it appears that the lack of the ketal moiety favours, for R = aryl, the intramolecular aldol reaction of **13** (Scheme 3, pathway on the left). The formation of the β-alkynylated ketone **15** through the enolate Smiles rearrangement can be completely suppressed. On the other hand, product **15** was obtained in previous work selectively for aryl substituents, by performing a protecting reaction before applying the basic conditions. Therefore, the reaction outcome for R = aryl is tuneable, whereas for aliphatic substituents, the formation of the bicyclic structure **4** is always preferred.

Applications and transformations: The importance of bicyclo[2.2.2]oct-5-en-2-ones **4** in synthetic organic chemistry is outlined in Figure 1. To further prove the value of these optically active compounds, different transformations were conducted for the 6-alkyl and 6-aryl substituted bicycles **4a** and **4d**, respectively (Scheme 6). The reduction of the double bond by palladium-catalysed hydrogenation resulted, in both cases (R = alkyl **18**, aryl **19**) as a 1:3 mixture of diastereoisomers, which could be separated by column chromatography. NOE measurements confirmed the major diastereoisomers to be **18** and **19**, rationalised through attack opposite the methylene bridge, which provides more steric bulk than the flat carbonyl moiety. In addition, pre-coordination of palladium to the carbonyl functionality could also



Scheme 6. Reduction and ring-expansion reactions of **4a** and **4d**.

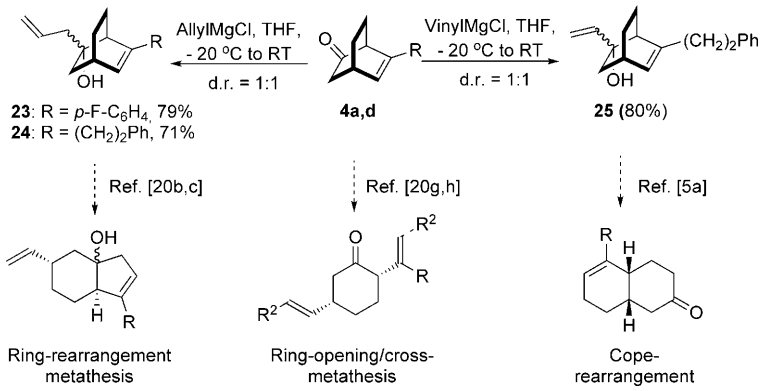
account for the stereochemical outcome. Similarly, the reduction of the ketone functionality with $NaBH_4$ gave a 1:2 mixture of inseparable isomers **22** in quantitative yield. The major isomer was assumed to result from attack opposite the methylene bridge, in analogy with the hydrogenation reaction previously discussed.

Two different ring-expanding reactions were performed, starting from enantio- and diastereomerically pure **18**, to confirm that regioselective access to either bicyclic lactones or lactams (Scheme 6) is possible. Treatment of **18** with *meta*-chloroperbenzoic acid (*m*CPBA) resulted in the ring-expanding Baeyer–Villiger oxidation. Surprisingly, the insertion of the oxygen atom occurred in both possible positions, resulting in a 1:1 mixture of 2-oxabicyclo[3.2.2]nonan-3-one **20a** and 3-oxa-bicyclo-[3.2.2]nonan-2-one **20b**. This effect has been reported earlier in literature.[17] On the other hand, the Schmidt reaction[18] of **4d** gave exclusively the 3-aza-bicyclo[3.2.2]nonan-2-one **21**.

As outlined before, bicyclo[2.2.2]octenones have been often utilised for the anionic oxy-Cope rearrangement.[5] Therefore, our aim was to transform **4a** into the required precursor for this rearrangement process (Scheme 7). Nucleophilic attack of vinylmagnesium chloride at the ketone carbonyl group gave the corresponding tertiary alcohol **25** in 80% yield. However, an inseparable 1:1 mixture of diastereoisomers was obtained. Since only one of the isomers underwent the subsequent [3,3]-sigmatropic rearrangement, it should be possible to resolve the mixture into the unreacted isomer and the chiral decalin structure.[5a]

Various bicycles of different sizes have been shown to be suitable substrates for metathesis reactions.[19] The release of ring strain as a driving force for these processes was exploited in ring-rearrangement metathesis (RRM) reactions, as well as in ring-opening metathesis polymerisation (ROMP) or ring-opening metathesis–cross metathesis (ROM–CM). Compounds **23** and **24**, chosen as adequate substrates for RRM, were thus synthesised by the addition of allylmagnesium chloride to **4a** or **4d**, respectively. Unfortunately, also in this case only a 1:1 mixture of diastereoisomers could be obtained. On the other hand, application of the chiral bicyclo[2.2.2]octenones **4** in ROMP would give access to enantiopure polymers. Due to the different substitution pattern on the olefinic side, selective ROM–CM processes can be also considered, depending on the catalytic species utilised. An overview of these possible applications is given in Scheme 7.

Finally, a stereoselective approach to chiral 5-hydroxybicyclo[2.2.2]octanes has been achieved, further demonstrating the versatility of transformations performable with the

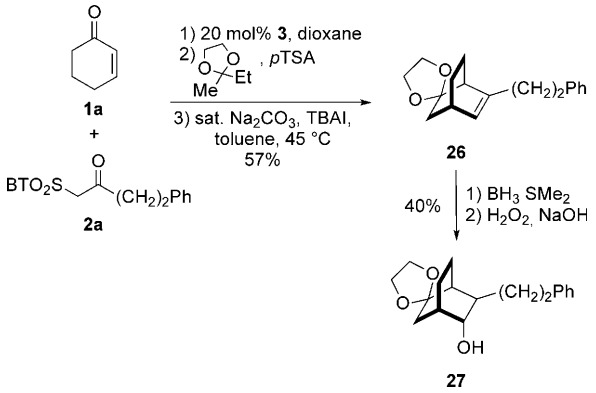


Scheme 7. Possible applications of chiral bicyclo[2.2.2]octenones **4**.

presented method. This compound class has been recently transformed into a new ligand class (BODOL), which proved to be efficient in asymmetric titanium-catalysed catecholborane reductions.[20] As outlined earlier, the cyclisation with aliphatic R substituents can be performed directly in the presence of a ketal group. Compound **26** was therefore synthesised directly, by applying the developed two-step sequence in an overall yield of 57% (Scheme 8). The protected ketone moiety enables subsequent hydroboration of the double bond, giving rise to **27** as a single diastereoisomer. The stereochemical outcome of this *syn* addition can be rationalised by coordination of borane to the ketal oxygen, resulting in an attack from the lower side, in analogy to the hydrogenation process (Scheme 6).

Conclusion

We have presented an easy, mild and organocatalytic approach to form highly enantioenriched 6-alkyl- and 6-aryl-substituted bicyclo[2.2.2]oct-5-en-2-ones, by applying a two-step sequence. The reaction can be also performed in a one-pot procedure without loss of enantioselectivity. The bicycles obtained, which are present in an array of natural products, were transformed into different building blocks, to be used in, for example, ligand synthesis or rearrangement reactions.



Scheme 8. Synthesis of chiral 5-hydroxybicyclo[2.2.2]octane **27**.

Experimental Section

General: ^{1}H and ^{13}C NMR spectra were acquired on a Varian AS 400 spectrometer, running at 400 and 100 MHz, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals ($CHCl_3$, $\delta=7.26$ ppm for ^{1}H NMR; $CDCl_3$, $\delta=77.0$ ppm for ^{13}C NMR). The following abbreviations are used to indicate the multiplicity in ^{1}H NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. ^{13}C NMR spectra were acquired on a broad-band decoupled mode. For characterisation of diastereomeric mixtures, *denotes minor diastereoisomer, $^+$denotes overlap of signals from both diastereoisomers. For approximately 1:1 mixtures of diastereoisomers, no individual characterisation is made. Mass spectra were recorded on a micromass LCT spectrometer by using electrospray (ES^+) ionisation techniques. Analytical TLC was performed by using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualised by ultraviolet irradiation or $KMnO_4$ dip. Melting points are uncorrected. Optical rotations were measured on a Perkin–Elmer 241 polarimeter. The *ee* value of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AS/AD and Daicel Chiralcel OD/OJ columns).

Materials: Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification. For flash chromatography (FC), Iatrobeads (6R6S-8060) were used. Nucleophiles **2a–f**,[13a] enone **1d**[13a] and catalysts **3**[12] were synthesised according to literature procedures. Racemic samples were prepared by using a racemic mixture of the catalyst.

General procedure for the synthesis of bicycles 4: An ordinary vial equipped with a magnetic stirring bar was charged with the nucleophile **2** (0.5 mmol, 1 equiv), the catalyst **3** (0.1 mmol, 0.2 equiv) and dioxane (5 mL). Upon complete dissolution of the catalyst, enone **1** (1.0 mmol, 2.0 equiv) was added. The reaction mixture was stirred until complete conversion of the nucleophile, as monitored by TLC or NMR spectroscopy (usually 24–48 h). Solvents were then removed in vacuo and the Michael adduct was purified on a short pad of Iatrobeads. The intermediate obtained was re-dissolved in a 1:1 mixture of toluene, and a saturated aqueous solution of Na_2CO_3 (10 mL) and TBAI (0.6 mmol, 1.2 equiv) was added. The biphasic suspension was vigorously stirred for 24 h at 45 °C and then diluted with H_2O (10 mL) and extracted with EtOAc (3× 10 mL). The combined organic phases were dried over $MgSO_4$, concentrated in vacuo and purified by FC on Iatrobeads.

*(1S,4S)-6-Phenethylbicyclo[2.2.2]oct-5-en-2-one (**4a**)*: Prepared by following the general procedure. Purification by FC (gradient: pentane to pentane/EtOAc 2:1) gave **4a** as a colourless oil (58% yield). $[\alpha]_D=-103.1$ ($c=1.0$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.30$–7.24 (m, 2H), 7.21–7.13 (m, 3H), 6.05 (d, $J=6.6$ Hz, 1H), 3.08–3.05 (m, 1H), 2.92–2.87 (m, 1H), 2.80–2.65 (m, 2H), 2.47–2.40 (m, 2H), 2.01–1.99 (m, 2H), 1.90–1.82 (m, 1H), 1.72–1.63 (m, 1H), 1.61–1.52 (m, 1H), 1.52–1.43 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=213.4$, 141.4, 140.6, 129.3, 128.3(2C), 128.3(2C), 125.9, 52.8, 41.1, 36.1, 33.9, 32.0, 24.9, 22.4 ppm; HRMS: m/z: calcd for $C_{16}H_{18}O+Na^+$: 249.1255 [$M+Na^+$]; found: 249.1252. The *ee* value was determined by HPLC using a Chiralpak AS column [hexane/*i*PrOH (98:2)]; flow rate 1.0 mL min^{-1}; $\tau_{major}=13.4$ min, $\tau_{minor}=11.7$ min (95% ee).

*(1S,4S)-6-Phenylbicyclo[2.2.2]oct-5-en-2-one (**4b**)*: Prepared by following the general procedure. Purification by FC (gradient: pentane to pentane/EtOAc 2:1) gave **4b** as a colourless oil (51% yield). $[\alpha]_D=-131.0$ ($c=0.22$ in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.43$–7.27 (m, 5H), 6.72 (d, $J=6.7$ Hz, 1H), 3.72–3.69 (m, 1H), 3.17–3.12 (m, 1H), 2.15–2.12 (m, 2H), 2.04–1.98 (m, 1H), 1.84–1.61 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=212.7$, 140.1, 137.4, 130.7, 128.6(2C), 127.5, 125.1(2C), 51.1, 40.6, 32.6, 24.6, 22.8 ppm; HRMS: m/z: calcd for $C_{14}H_{14}O+Na^+$: 221.0942 [$M+Na^+$]; found: 221.0945. The *ee* value was determined by HPLC using a Chiralpak AS column (hexane/*i*PrOH (98:2)); flow rate 1.0 mL min^{-1}; $\tau_{major}=16.2$ min, $\tau_{minor}=14.0$ min (91% ee).

*(1S,4S)-6-(3-Chlorophenyl)bicyclo[2.2.2]oct-5-en-2-one (**4c**)*: Prepared by following the general procedure. Purification by FC (gradient: pentane to pentane/EtOAc 2:1) gave **4c** (49% yield) as a colourless oil. $[\alpha]_D=-66.0$ ($c=0.32$ in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.39$–7.37 (m, 1H), 7.28–7.23 (m, 3H), 6.75 (d, $J=6.8$ Hz, 1H), 3.67–3.63 (m, 1H), 3.18–3.14 (m, 1H), 2.14–2.12 (m, 2H), 2.07–1.98 (m, 1H), 1.83–1.61 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=212.1$, 139.2, 139.0, 134.6, 132.0, 129.8, 127.5, 125.3, 123.2, 51.0, 40.4, 32.6, 24.5, 22.7 ppm; HRMS: m/z: calcd for $C_{14}H_{13}ClO+Na^+$: 255.0553 [$M+Na^+$]; found: 255.0544. The *ee* value was determined by HPLC using a Chiralpak AS column (hexane/*i*PrOH (98:2)); flow rate 1.0 mL min^{-1}; $\tau_{major}=14.8$ min, $\tau_{minor}=13.7$ min (95% ee).

*(1S,4S)-6-(4-Fluorophenyl)bicyclo[2.2.2]oct-5-en-2-one (**4d**)*: Prepared by following the general procedure. Purification by FC (gradient: pentane to pentane/EtOAc 2:1) gave **4d** as a colourless oil (44% yield). $[\alpha]_D=-162.0$ ($c=0.25$ in MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.39$–7.32 (m, 2H), 7.02 (app. t, $J=6.8$ Hz, 2H), 6.66 (d, $J=6.7$ Hz, 1H), 3.66–3.63 (m, 1H), 3.17–3.11 (m, 1H), 2.14–2.12 (m, 2H), 2.05–1.97 (m, 1H), 1.84–1.60 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=212.5$, 162.3 (d, $J=245.6$ Hz), 139.1, 133.6 (d, $J=3.2$ Hz), 130.4, 126.7 (d, $J=8.0$ Hz, 2C), 115.5 (d, $J=21.4$ Hz, 2C), 51.3, 40.5, 32.5, 24.6, 22.7 ppm; HRMS: m/z: calcd for $C_{14}H_{13}FO+Na^+$: 239.0848 [$M+Na^+$]; found: 239.0843. The *ee* value was determined by HPLC using a Chiralpak AS column (hexane/*i*PrOH (98:2)); flow rate 1.0 mL min^{-1}; $\tau_{major}=17.5$ min, $\tau_{minor}=12.8$ min (94% ee).

*(1S,4S)-6-p-Tolylbicyclo[2.2.2]oct-5-en-2-one (**4e**)*: Prepared by following the general procedure. Purification by FC (gradient: pentane to pentane/EtOAc 2:1) gave **4e** as a colourless oil (50% yield). $[\alpha]_D=-39.6$ ($c=1.21$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.30$ (d, $J=8.0$ Hz, 2H), 7.14 (d, $J=7.9$ Hz, 2H), 6.67 (d, $J=6.8$ Hz, 1H), 3.70–3.67 (m, 1H), 3.15–3.10 (m, 1H), 2.34 (s, 3H), 2.14–2.11 (m, 2H), 2.05–1.96 (m, 1H), 1.83–1.63 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=212.8$, 139.9, 137.4, 134.6, 129.7, 129.3(2C), 124.9(2C), 51.1, 40.7, 32.5, 24.6, 22.8, 21.1 ppm; HRMS: m/z: calcd for $C_{15}H_{16}O+Na^+$: 235.1098 [$M+Na^+$]; found: 235.1099. The *ee* value was determined by HPLC using a Chiralpak AS column (hexane/*i*PrOH (97:3)); flow rate 1.0 mL min^{-1}; $\tau_{major}=7.8$ min, $\tau_{minor}=8.2$ min (94% ee).

*(1S,4S)-6-(Naphthalen-2-yl)bicyclo[2.2.2]oct-5-en-2-one (**4f**)*: Prepared by following the general procedure. Purification by FC (gradient: pentane to pentane/EtOAc 2:1) gave **4f** as a colourless oil (59% yield). $[\alpha]_D=-83.3$ ($c=0.68$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.85$–7.76 (m, 4H), 7.60–7.54 (m, 1H), 7.50–7.42 (m, 2H), 6.87 (d, $J=6.5$ Hz, 1H), 3.88 (app. s, 1H), 3.22–3.17 (m, 1H), 2.20–2.16 (m, 2H), 2.10–2.05 (m, 1H), 1.90–1.65 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=212.7$, 139.9, 134.4, 132.8, 131.2, 129.6, 128.3, 128.1, 127.5, 126.4, 126.0, 123.6, 123.3, 51.0, 40.7, 32.7, 24.7, 22.8 ppm; HRMS: m/z: calcd for $C_{18}H_{16}O+Na^+$: 271.1098 [$M+Na^+$]; found: 271.1099. The *ee* value was determined by HPLC using a Chiralpak AS column (hexane/*i*PrOH (98:2)); flow rate 1.0 mL min^{-1}; $\tau_{major}=12.8$ min, $\tau_{minor}=13.6$ min (97% ee).

*(1S,4S)-6-Phenylbicyclo[2.2.1]hept-5-en-2-one (**4g**)*: Prepared by following the general procedure. Purification by FC (gradient: pentane to pentane/EtOAc 2:1) gave **4g** as a colourless oil (44% yield). $[\alpha]_D=-46.3$ ($c=1.1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.45$–7.40 (m, 2H),

7.35–7.29 (m, 3H), 6.72 (d, $J=2.9$ Hz, 1H), 3.49 (app. s, 1H), 3.31 (app. s, 1H), 2.43–2.38 (m, 1H), 2.13 (d, $J=9.3$ Hz, 1H), 2.08 (d, $J=3.3$ Hz, 1H), 2.00 (d, $J=4.3$ Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=215.2$, 144.2, 135.3, 128.6(2C), 127.8, 127.2, 125.1(2C), 57.8, 50.1, 40.6, 37.8 ppm; HRMS: m/z: calcd for $C_{13}H_{12}O+Na^+$: 207.0786 [$M+Na^+$]; found: 207.0797. The *ee* value was determined by HPLC using a Chiralpak AS column (hexane/*i*PrOH (98:2)); flow rate 1.0 mL min^{-1}; $\tau_{major}=8.6$ min, $\tau_{minor}=11.1$ min (60% ee).

*(S)-3-((4-Fluorophenyl)ethynyl)cycloheptanone (**4h**)*: Prepared by following the general procedure, but by performing the organocatalytic step at 45 °C and the cyclisation step at 65 °C. Purification by FC (gradient: pentane to pentane/EtOAc 2:1) gave **4h** as a colourless oil (51% yield). $[\alpha]_D=+6.6$ ($c=1.3$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.37$–7.33 (m, 2H), 6.97 (t, $J=8.8$ Hz, 2H), 3.11–3.05 (m, 1H), 2.79 (d, $J=5.8$ Hz, 2H), 2.68–2.49 (m, 2H), 2.07–1.90 (m, 3H), 1.83–1.67 ppm (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=212.3$, 162.2 (d, $J=247.3$ Hz), 133.3 (d, $J=8.3$ Hz, 2C), 119.3 (d, $J=3.6$ Hz), 115.4 (d, $J=21.8$ Hz, 2C), 90.6 (d, $J=1.5$ Hz), 82.4, 48.8, 44.0, 36.3, 27.8, 27.3, 23.9 ppm; HRMS: m/z: calcd for $C_{15}H_{15}FO+Na^+$: 253.1004 [$M+Na^+$]; found: 253.1005. The *ee* value was determined by HPLC using a Chiralpak AS column (hexane/*i*PrOH (98:2)); flow rate 1.0 mL min^{-1}; $\tau_{major}=23.5$ min, $\tau_{minor}=20.5$ min (98% ee).

(1*R*,4*S*,5*S*,6*R*)-5-(Benzo[*d*]thiazol-2-yloxy)-2,2-dimethyl-6-phenylbicyclo-[2.2.2]octan-7-one (*trans*-16): Prepared by following the general procedure. Purification by FC (gradient: pentane to pentane/EtOAc 2:1) gave **16** as a colourless oil (54% yield, d.r. 5:95). $[\alpha]_D=-4.7$ ($c=1.0$ in CH_2Cl_2); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.99$ (d, $J=8.2$ Hz, 1H), 7.87 (app. d, $J=7.2$ Hz, 3H), 7.55–7.35 (m, 5H), 5.32 (s, 1H), 3.51–3.43 (m, 1H), 3.16 (dd, $J=8.6$, 17.9 Hz, 1H), 2.99 (dd, $J=3.3$, 18.0 Hz, 1H), 2.81 (d, $J=12.4$ Hz, 1H), 2.70 (dd, $J=0.9$, 12.4 Hz, 1H), 1.79–1.64 (m, 2H), 1.24 (s, 3H), 1.10 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=208.0$, 172.5, 152.5, 136.7, 135.9, 133.3, 128.5(2C), 128.1(2C), 126.0, 125.2, 123.1, 121.8, 82.1, 49.2, 40.6, 39.4, 38.7, 35.3, 31.4, 27.6(2C) ppm; HRMS: m/z: calcd for $C_{23}H_{23}KNO_2S^+$: 416.1087 [$M+H^+$]; found: 416.1250.

(1*R*,4*S*,5*S*,6*S*)-5-(Benzo[*d*]thiazol-2-yloxy)-2,2-dimethyl-6-phenethylbicyclo[2.2.2]octan-7-one (*trans*-17): Prepared by following the general procedure. Purification by FC (gradient: pentane to pentane/EtOAc 2:1) gave **17** as a colourless oil (59% yield, d.r. 1:1). $[\alpha]_D=+10.7$ ($c=2.1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=8.08$–8.03 (m, 2H), 7.89–7.85 (m, 2H), 7.54–7.47 (m, 2H), 7.42–7.36 (m, 2H), 7.28–7.20 (m, 10H), 5.19–5.16 (m, 2H), 3.64 (s, 4H), 3.23–3.09 (m, 2H), 2.77–2.61 (m, 2H), 2.39–2.28 (m, 2H), 2.28–2.19 (m, 1H), 2.08–1.97 (m, 4H), 1.80 (t, $J=14.0$ Hz, 1H), 1.63 (t, $J=13.2$ Hz, 1H), 1.43 (d, $J=13.2$ Hz, 1H), 1.29–1.16 (m, 4H), 0.97 (s, 3H), 0.81 (s, 3H), 0.80 (s, 3H), 0.69 ppm (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=206.6$, 206.5, 172.9, 172.8, 153.3, 153.2, 135.7, 135.7, 134.3, 134.2, 130.2(2C), 130.2(2C), 128.2(2C), 128.2(2C), 127.3, 127.3, 126.2(2C), 125.3(2C), 123.0, 123.0, 121.9, 121.8, 84.4, 84.3, 60.3(2C), 54.1(2C), 46.4, 46.0, 44.7, 44.6, 44.4, 44.1, 43.1, 43.1, 34.9, 34.7, 31.8, 31.6, 30.4, 30.2, 25.4, 25.3 ppm.

(1*S*,4*R*)-6-(4-Fluorophenyl)bicyclo[2.2.2]octan-2-one (18): A suspension of compound **4d** (0.2 mmol) and 20% $Pd(OH)_2$/C (15 mg) in MeOH (1.5 mL) was stirred under a hydrogen atmosphere at 20 °C for 12 h. The reaction mixture was filtered through a pad of silica and the filtrate was concentrated under reduced pressure. Purification of the residue by FC (gradient: pentane to pentane/EtOAc 4:1) afforded compound **18** as a colourless oil (94% yield, d.r. 1:3). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.11$–7.05 (m, 2H), 6.98–6.92 (m, 2H), 3.30–3.20 (m, 1H), 2.45–2.26 (m, 5H), 2.01–1.61 ppm (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=216.2$, 216.2*, 161.5* (d, $J=243.5$ Hz), 161.3 (d, $J=243.1$ Hz), 141.2 (d, $J=3.0$ Hz), 137.8* (d, $J=3.3$ Hz), 129.1* (d, $J=7.8$ Hz, 2C), 128.3 (d, $J=7.9$ Hz, 2C), 115.3$^+$ (d, $J=21.1$ Hz, 4C), 49.2*, 48.7, 45.2, 43.5*, 41.8, 37.4*, 35.1, 30.9*, 28.3*, 27.7, 25.2*, 24.3, 23.2, 17.3* ppm; HRMS: m/z: calcd for $C_{14}H_{15}FO+Na^+$: 241.1006 [$M+Na^+$]; found: 241.1005.

(1*S*,4*R*)-6-Phenethylbicyclo[2.2.2]octan-2-one (19): Prepared by following the same procedure as above for compound **18**, compound **19** was isolated (81% yield, d.r. 1:3) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.29$–7.24 (m, 2H), 7.20–7.13 (m, 3H), 2.62 (t, $J=7.8$ Hz, 2H), 2.27–2.15 (m, 4H), 2.05–1.86 (m, 3H), 1.84–1.76 (m, 2H), 1.67–1.43 (m, 5H), 1.31–1.16 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=217.0$, 141.9, 141.8, 128.4 (2C), 128.4 (2C), 128.3(2C), 128.3(2C), 125.9, 125.8, 47.5, 46.8, 44.8, 43.6, 39.1, 36.1, 35.6, 33.6, 33.4, 33.0, 32.7, 31.9, 28.2, 28.1, 25.2, 23.8, 23.3, 17.5 ppm; HRMS: m/z: calcd for $C_{16}H_{20}O+Na^+$: 251.1412 [$M+Na^+$]; found: 251.1412.

(1*S*,5*R*,7*R*)-7-(4-Fluorophenyl)-2-oxabicyclo[3.2.2]nonan-3-one and (1*S*,5*R*,7*S*)-7-(4-fluorophenyl)-3-oxabicyclo[3.2.2]nonan-2-one (20a and 20b): *m*CPBA (0.8 mmol, 4 equiv) was added to a stirred solution of **18** (0.2 mmol) in CH_2Cl_2 (0.5 mL) at 0 °C. Upon completion of the reaction, the reaction mixture was diluted with EtOAc (5 mL), washed with a saturated aqueous solution of sodium thiosulfate (2 mL) and brine (2 mL). The organic phase was dried over $MgSO_4$, concentrated in vacuo and purified by FC on silica gel (gradient: pentane/EtOAc 4:1 to pentane/EtOAc 2:1) to afford the regioisomers **20a** and **20b** as a colourless oil (60% combined yield, ratio 1:1). $[\alpha]_D=-1.5$ ($c=0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.30$–7.23 (m, 4H), 7.04–6.97 (m, 4H), 4.56–4.28 (m, 2H), 3.13–2.73 (m, 6H), 2.44–2.19 (m, 6H), 2.12–2.00 (m, 2H), 1.90–1.71 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=173.7$ (2C), 161.8 (d, $J=243.5$ Hz, 2C), 138.4 (d, $J=3.8$ Hz, 2C), 129.3 (d, $J=7.8$ Hz, 2C), 128.8 (d, $J=7.9$ Hz, 2C), 115.4 (d, $J=21.1$ Hz, 2C), 115.3 (d, $J=21.0$ Hz, 2C), 78.2, 75.2, 47.0, 42.7, 42.3, 39.8, 32.7, 31.3, 30.5, 28.1, 25.4, 24.2, 23.7, 22.7 ppm; HRMS: m/z: calcd for $C_{14}H_{15}FO_2+Na^+$: 257.0954 [$M+Na^+$]; found: 257.0951.

(1*S*,5*R*,7*S*)-7-(4-Fluorophenyl)-3-azabicyclo[3.2.2]nonan-2-one (21): NaN_3 (0.09 mmol, 1.2 equiv, in 30 μL H_2O) was carefully added to a stirred solution of **18** (0.08 mmol, 1.0 equiv) in TFA (0.8 mL). The reaction mixture was stirred at RT for 30 min and then heated at 50 °C for 4 h. Upon completion of the reaction, H_2O and solid $NaHCO_3$ were carefully added and the aqueous phase was extracted with EtOAc (3×5 mL). The combined organic phases were dried over $MgSO_4$, concentrated in vacuo and purified by FC on silica gel (gradient: pentane/EtOAc 4:1 to pure EtOAc) to give **21** as a colourless oil (90% yield). $[\alpha]_D=-9.5$ ($c=0.5$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.19$ (dd, $J=5.3$, 8.7 Hz, 2H), 6.95 (s, 1H), 6.89 (t, $J=8.7$ Hz, 2H), 3.25 (app. s, 2H), 3.05 (app. s, 1H), 2.97 (dt, $J=2.6$, 9.7 Hz, 1H), 2.47–2.42 (m, 1H), 2.32–2.15 (m, 2H), 2.02–1.70 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=179.0$, 161.6 (d, $J=243.0$ Hz), 139.6 (d, $J=3.0$ Hz), 129.0 (d, $J=7.8$ Hz, 2C), 115.1 (d, $J=20.9$ Hz, 2C), 49.3, 46.2, 41.0, 31.7, 29.2, 24.7, 24.3 ppm; HRMS: m/z: calcd for $C_{14}H_{16}NFO+Na^+$: 256.1114 [$M+Na^+$]; found: 256.1117.

(1*S*,4*S*)-6-Phenethylbicyclo[2.2.2]oct-5-en-2-ol (22): $NaBH_4$ (0.05 mmol, 1.5 equiv) was added to a stirred solution of **4a** (0.03 mmol) in THF (1 mL) at 0 °C, followed by MeOH (0.3 mL). The mixture was stirred for 1 h, then quenched by the addition of a saturated aqueous solution of NH_4Cl and extracted with CH_2Cl_2. After drying over $MgSO_4$ the solvent was removed in vacuo and the residue purified by FC (gradient: pentane to pentane/EtOAc 3:1) to provide **22** as a colourless oil (99% yield, d.r. 1:2). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.30$–7.26$^+$ (m, 4H), 7.23–7.16$^+$ (m, 6H), 6.05 (dd, $J=1.4$, 6.6 Hz, 1H), 5.88* (dd, $J=1.4$, 6.4 Hz, 1H), 3.97–3.92 (m, 1H), 3.85–3.80* (m, 1H), 2.83–2.37$^+$ (m, 12H), 2.08–1.89$^+$ (m, 2H), 1.43–1.05$^+$ ppm (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=142.1$, 141.8*, 128.4, 128.3*, 128.3$^+$(4C), 128.3$^+$(2C) 127.5, 127.3*, 125.8$^+$(4C), 70.7, 69.6*, 42.3*, 42.1, 39.2, 37.8, 36.7*, 36.5*, 34.1*, 33.9, 30.4*, 29.8, 26.7*, 24.8, 21.8, 17.4* ppm; HRMS: m/z: calcd for $C_{16}H_{20}O+Na^+$: 251.1411 [$M+Na^+$]; found: 251.1412.

General procedure for the Grignard addition: A dry Schlenk tube was charged with compound **4** (0.2 mmol) and THF (1.5 mL) and cooled to −20 °C. The Grignard reagent (1 M solution in THF, 0.25 mmol, 1.25 equiv) was added dropwise by syringe at −20 °C. The mixture was allowed to warm to RT over a period of 2 h, and stirred overnight, before a saturated aqueous solution of NH_4Cl (1 mL) was added, followed by a 2 N aqueous solution of HCl (1 mL). The organic layer was extracted with EtOAc (2×3 mL). The combined organic layers were dried over $MgSO_4$, concentrated and purified by FC (gradient: pentane to pentane/EtOAc 2:3) to afford the corresponding tertiary alcohols.

*(1S,4S)-2-Allyl-6-(4-fluorophenyl)bicyclo[2.2.2]oct-5-en-2-ol (**23**)*: Following the general procedure, treatment of **4d** with allylmagnesium chloride gave **23** (79% yield, d.r. 1:1) as a colourless oil. ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.45$–7.36$^+$ (m, 4H), 7.05–6.98$^+$ (m, 4H), 6.57* (dd, $J=1.6$,

6.7 Hz, 1H), 6.46 (dd, $J=1.6$, 6.7 Hz, 1H), 6.09–5.98* (m, 1H), 5.79 (ddt, $J=1.4$, 10.2, 17.5 Hz, 1H), 5.23–4.96$^+$ (m, 4H), 3.07–3.05* (m, 1H), 2.93–2.90 (m, 1H), 2.79–2.72$^+$ (m, 2H), 2.53* (ddt, $J=1.2$, 6.7, 14.0 Hz, 1H), 2.40* (dd, $J=14.0$, 7.7 Hz, 1H), 2.32–2.24 (m, 1H), 2.14–2.09$^+$ (m, 2H), 2.18–2.06 (m, 1H), 1.81–1.65$^+$ (m, 4H), 1.58–1.16$^+$ ppm (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=162.1$* (d, $J=244.1$ Hz), 162.0 (d, $J=244.3$ Hz), 143.2, 142.6*, 135.8* (d, $J=3.3$ Hz), 135.1 (d, $J=2.9$ Hz), 134.3*, 133.3, 128.7*, 128.1, 126.6* (d, $J=7.7$ Hz, 2C), 126.2 (d, $J=7.7$ Hz, 2C), 119.7, 118.2*, 115.3 (d, $J=21.2$ Hz, 2C), 115.2* (d, $J=21.1$ Hz, 2C), 75.1, 74.9*, 47.4, 44.8*, 44.7*, 43.8, 43.6*, 41.4, 31.8, 31.3*, 24.9, 23.9*, 21.0*, 20.0 ppm; HRMS: m/z: calcd for $C_{17}H_{19}FO+Na^+$: 281.1318 [$M+Na^+$]; found: 281.1318.

*(1S,4S)-2-Allyl-6-phenethylbicyclo[2.2.2]oct-5-en-2-ol (**24**)*: Following the general procedure, treatment of **4a** with allylmagnesium chloride gave **24** as a colourless oil (71% yield, d.r. 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 7.31–7.26 (m, 2H), 7.23–7.16 (m, 3H), 6.02–5.84 (m, 2H), 5.21–5.08 (m, 2H), 2.88–2.65 (m, 2H), 2.56–2.51 (m, 1H), 2.49–2.40 (m, 3H), 2.36–2.27 (m, 1H), 2.19–2.07 (m, 2H), 1.68–1.02 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=145.0$, 144.4, 142.2, 134.6, 133.7, 128.3, 128.3, 126.5, 125.8, 125.7, 125.6, 119.4, 117.9, 75.0, 74.9, 47.5, 45.6, 45.1, 44.9, 44.7, 42.2, 37.7, 37.0, 33.8, 33.7, 31.1, 30.7, 25.2, 24.7, 21.0, 19.9 ppm; HRMS: m/z: calcd for $C_{19}H_{24}O+Na^+$: 291.1725 [$M+Na^+$]; found: 291.1728.

*(1S,4S)-6-Phenethyl-2-vinylbicyclo[2.2.2]oct-5-en-2-ol (**25**)*: Following the general procedure, treatment of **4a** with vinylmagnesium chloride gave **25** as a colourless oil (80% yield, d.r. 1:1). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.30$–7.26 (m, 2H), 7.23–7.17 (m, 3H), 6.09–5.79 (m, 2H), 5.38–4.90 (m, 2H), 2.80–2.33 (m, 6H), 1.73–1.10 ppm (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=146.9$, 144.8, 142.6, 142.1, 129.7, 128.6, 128.6, 128.5, 128.5, 128.0, 127.0, 126.3, 126.1, 126.0, 112.9, 110.1, 76.1, 76.1, 47.3, 47.2, 43.6, 42.6, 38.0, 37.3, 34.0, 31.0, 30.8, 25.4, 25.2, 20.9, 20.1 ppm.

(1S,4S)-6-phenethylspiro[bicyclo[2.2.2]oct[5]-ene-2,2′-[1,3]-dioxolane] (26): An ordinary vial equipped with a magnetic stirring bar was charged with the nucleophile **2a** (0.5 mmol, 1 equiv), the catalyst **3** (0.1 mmol, 0.2 equiv) and dioxane (5 mL). Upon complete dissolution of the catalyst, enone **1a** (1.0 mmol, 2.0 equiv) was added. The reaction mixture was stirred for 48 h. Solvents were removed in vacuo and the Michael adduct **5a** was purified on a short pad of Iatrobeads. The obtained intermediate was dissolved in toluene (1 mL), treated with 2-ethyl-2-methyl-1,3-dioxolane (15 mmol, 30 equiv) and *p*TSA (0.15 mmol, 0.3 equiv). After stirring for 24 h, the mixture was diluted with EtOAc, washed with a saturated aqueous solution of $NaHCO_3$ and concentrated in vacuo. The obtained residue was re-dissolved in a 1:1 mixture of toluene and a saturated aqueous solution of Na_2CO_3 (10 mL), and TBAI (0.6 mmol, 1.2 equiv) was added. The biphasic suspension was vigorously stirred for 24 h at 45°C and then diluted with H_2O (10 mL) and extracted with EtOAc (3× 10 mL). The combined organic phases were dried over $MgSO_4$, concentrated in vacuo and purified by FC on Iatrobeads (gradient: pentane to pentane/EtOAc 4:1) to give **26** as a colourless oil (57% yield over 3 steps). $[\alpha]_D=-16.7$ ($c=0.9$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=$ 7.31–7.16 (m, 5H), 5.93 (dd, $J=1.4$, 6.5 Hz, 1H), 3.94–3.90 (m, 4H), 2.80–2.75 (m, 2H), 2.62–2.57 (m, 1H), 2.50–2.32 (m, 3H), 1.94–1.83 (m, 2H), 1.74–1.30 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=144.0$, 142.4, 131.3, 128.3(2C), 128.2(2C), 125.9, 125.7, 64.0, 63.9, 42.5, 41.2, 37.1, 33.8, 30.8, 24.9, 20.5 ppm.

(1S,4S,5R,6R)-6-Phenethylspiro[bicyclo[2.2.2]-octane-2,2′-[1,3]-dioxolan]-5-ol (27): BH_3-Me_2S (0.08 mmol, 1.5 equiv) was added dropwise to a stirred solution of **26** (0.06 mmol) in THF (0.3 mL) at 0°C. The reaction mixture was stirred for 3 h at 0°C and then allowed to reach RT overnight. A 3 N aqueous solution of NaOH (20 μL) and a 30% aqueous solution of H_2O_2 (20 μL) were added and the solution was stirred for 4 h, then diluted with diethyl ether and washed with brine. After drying over $MgSO_4$, the organic phase was concentrated in vacuo and purified by FC (gradient: pentane to pentane/EtOAc 4:1) to give **27** as a pale yellow oil (40% yield over 2 steps). $[\alpha]_D=-12.0$ ($c=0.1$ in $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=7.30$–7.17 (m, 5H), 3.96–3.79 (m, 4H), 3.66–3.61 (m, 1H), 2.75–2.65 (m, 2H), 2.03–1.68 (m, 8H), 1.52–1.30 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=142.8$, 128.4(2C), 128.3(2C), 125.6, 110.5, 76.4, 64.1, 63.3, 46.4, 39.1, 36.5, 36.2, 35.0, 34.5, 23.3, 17.2 ppm; HRMS: m/z: calcd for $C_{18}H_{24}O_3+Na^+$: 311.1623 [$M+Na^+$]; found: 311.1624.

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