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Improved Synthesis of Cyclic Tertiary Allylic Alcohols by Asymmetric 1,2-Addition of $AlMe_3$ to Enones

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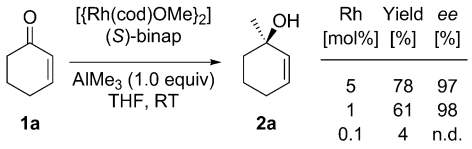
Abstract: The development of an improved protocol for the enantioselective Rh^I/binap-catalysed 1,2-addition of $AlMe_3$ to cyclic enones is reported. ^{31}P NMR analysis of the reaction revealed that the catalyst in its resting state is a chloride-bridged dimer. This insight led to the use of $AgBF_4$ as an additive for in situ activation of the dimeric precatalyst. Thus, the catalyst loading can now be reduced to only 1 mol% with respect to rhodium. Various 5–7-membered cyclic enones can be transformed into tertiary allylic alcohols with excellent levels of enantioselectivity and high yields. The obtained products are versatile synthetic building blocks, shown by a highly enantioselective formal total synthesis of the pheromone (−)-frontalin as well as formation of a bicyclic lactone that has the core structure of the natural flavour component "wine lactone".

Keywords: alanes · allylic alcohols · asymmetric catalysis · enones · nucleophilic addition · rhodium

Introduction

α,β-Unsaturated carbonyl compounds are highly versatile substrates for C–C bond formation in organic synthesis. The asymmetric conjugate addition (1,4-addition) of nucleophilic species to such compounds is one of the most intensively studied and well-established synthetic methods in organic chemistry.[1] In contrast, asymmetric 1,2-addition to α,β-unsaturated carbonyl compounds has been reported to a lesser extent, even though the products, chiral allylic alcohols, are very important. They occur as structural motifs in numerous target molecules and can take part in a broad range of reactions, in which additional stereocentres can be selectively assembled owing to effective stereoinduction by the hydroxy group.[2]

Among the protocols for asymmetric 1,2-addition, only a handful allow for the transformation of 2-enones.[3] In general, the transformation of ketones, in comparison with that of aldehydes, requires a more reactive nucleophile and more sophisticated stereodiscrimination by the catalyst. Moreover, the resulting tertiary allylic alcohols are less accessible than secondary ones, which can also be obtained through methods such as stereoselective reduction of C=O bonds.[2] Focussing on cyclic structures, which account for a large portion of target molecules, the number of available synthetic methods becomes even smaller. To the best of our knowledge, only two protocols exist for the asymmetric preparation of cyclic tertiary allylic alcohols from cycloalk-2-enones.[4] The research groups of Walsh and Yus have independently developed a $Ti(OiPr)_4$-mediated addition of organozinc reagents to ketones using a chiral bis(sulfonamide) ligand (hocsac).[5] However, when using cycloalkenones as substrates, a substituent in the 2-position is usually required to achieve high levels of selectivity.[5f,g] We have previously reported a Rh^I/binap-catalysed 1,2-addition furnishing excellent levels of enantioselectity and high yields of product even in the case of unsubstituted cycloalkenones (Scheme 1).[6] The utilisation of organoaluminium reagents



Scheme 1. Rh^I/binap-catalysed addition of $AlMe_3$ (n.d. = not determined).[6]

as nucleophiles is an attractive feature of this method.[7] Both inexpensive $AlMe_3$ and air-stable adduct DABCO-$(AlMe_3)_2$[8] (DABCO = 1,4-diazabicyclo[2.2.2]octane) can be used for the addition of a methyl group; aryl groups can be introduced from mixed alanes $ArAlMe_2$. The products of these addition reactions are either biologically active, for example, as pheromones,[9] or they serve as chiral building blocks (see below). We recently expanded this methodology to include classic kinetic resolution as well as regiodivergent reactions on racemic substituted cyclohex-2-enones.[10]

A drawback of the methodology described above is the need for a rather high catalyst loading of 5 mol% rhodium,

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that is, 2.5 mol% of dimeric precatalysts, such as [{Rh(cod)OMe}$_2$]. Lowering the amount of rhodium to 1 mol% led to a significantly lower yield; almost no product was formed when the amount of rhodium was reduced to 0.1 mol% (Scheme 1). The need for high catalyst loadings becomes particularly problematic in the case of multigram preparations,[11] even though the price of rhodium has dropped over the last 10 years and is now significantly lower than that of gold or platinum and approximately just 30% higher than that of palladium.[12] Herein, we report an improved catalytic system that affords excellent results for the synthesis of cyclic tertiary allylic alcohols using only 1 mol% rhodium. Moreover, applications of the resulting products in target structure syntheses are presented. These results broaden the scope of the described method in both an economic and a synthetic sense.

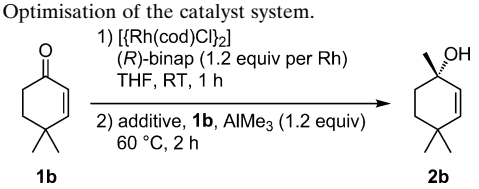
Results and Discussion

To gain some insight into the mechanism of the Rh^I/binap-catalysed 1,2-addition reaction, the transformation of cyclohexenone **1a** into product **2a** was followed by ^{31}P NMR spectroscopy and simultaneous GC analysis. During the reaction, the large majority of the detected phosphorous species was in fact dimeric complex [{Rh(binap)X}$_2$] (X = OMe, Cl), which is formed upon premixing the respective dimeric cycloocta-1,5-diene (cod) complex and the chiral phosphane. This binap complex must be a precatalyst that slowly liberates the catalytically active species. Thus, we speculated that promoting the cleavage of this dimer would provide the key to a more active catalyst, even though we previously observed inferior results with [Rh(cod)$_2$]BF$_4$ as rhodium source.[6] Fortunately, addition of a slight excess of AgBF$_4$ (based on the amount of chloride) led to a quantitative yield of the 1,2-addition product **2a** with just 0.5 mol% of dimeric [{Rh(binap)Cl}$_2$].

Abstract in German: *Die Entwicklung einer optimierten Vorschrift für die Rh^I/binap-katalysierte enantioselektive 1,2-Addition von AlMe$_3$ an cyclische Enone wird beschrieben. Eine Analyse des Reaktionsverlaufs mittels ^{31}P-NMR wies auf ein Chlorid-verbrücktes Dimer als Resting State des Katalysators hin; tatsächlich gelang eine in-situ-Aktivierung durch Zusatz von AgBF$_4$ als Additiv. Auf diese Weise kann die Katalysatorbeladung auf nur noch 1 mol% Rhodium reduziert werden. Die Methode erlaubt die Umsetzung verschiedener 5–7-gliedriger cyclischer Enone mit exzellenten Enantioselektivitäten und hohen Ausbeuten. Die erhaltenen tertiären Allylalkohole sind vielseitige Synthesebausteine und wurden zu einer hoch enantioselektiven formalen Totalsynthese von (−)-Frontalin und zur Bildung eines bicyclischen Lactons mit dem Grundgerüst des natürlichen Duftstoffs Weinlacton verwendet.*

For further experiments, 4,4-dimethylcyclohex-2-enone (**1b**) was chosen as the substrate because its transformation occurs almost as selectively as the transformation of **1a**, but the reaction is slower (Table 1).[6] In the absence of silver salts, the reaction proceeded smoothly using 5 mol% rhodium, whereas both the reaction rate and the chemoselectivity greatly decreased when only 1 mol% of rhodium was used, especially after a prolonged reaction time (Table 1, entries 1 and 2). With the same catalyst loading (1 mol%), high selectivity was once again obtained upon addition of AgBF$_4$ (Table 1, entry 3). Lowering the amount of rhodium to 0.5 mol% resulted in diminished reproducibility of the 1,2-addition and, interestingly, the beneficial effect of the silver salt was no longer observed (Table 1, entries 4 and 5). In the presence of a larger excess of AgBF$_4$, the product of the reaction was almost racemic (Table 1, entry 6). In the absence of any rhodium species, product **2b** was formed rather unselectively (Table 1, entry 7). Finally, using 1 mol% of [Rh(cod)$_2$]BF$_4$, in the absence of AgBF$_4$, or using 0.5 mol% of dimeric [{Rh(C$_2$H$_4$)$_2$Cl}$_2$], in the presence of excess AgBF$_4$, consistently led to inferior results (compare Table 1, entry 3 versus entries 8 and 9).

Table 1. Optimisation of the catalyst system.

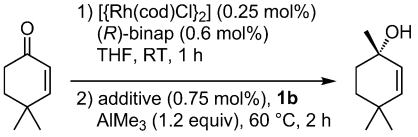


Entry	Rhodium [mol%][a]	Additive ([mol%])	Conv. [%][b]	Yield [%][b]	*ee* [%][b]
1	5	–	91	91	97
2	1	–	73±2[c]	64±2[c]	97±1
3	1	AgBF$_4$ (1.5)	97±1	88±2	97±1
4	0.5	–	58±2	47±8	89±1
5	0.5	AgBF$_4$ (0.75)	73±16	47±13	93±2
6	0.5	AgBF$_4$ (2.5)	64	23	5
7	0[d]	AgBF$_4$ (1.5)	28	6	n.d.
8	1[e]	–	94±1	75±1	96±1
9	1[f]	AgBF$_4$ (1.5)	97±0	78±1	93±1

[a] Actual amount of rhodium. [b] Determined by GC. Values with standard deviation represent the mean of 3–4 experiments. [c] After 24 h: 97% conv., 68% yield. [d] Performed with 1.2 mol% (*R*)-binap for 3 h. [e] [Rh(cod)$_2$]BF$_4$ as rhodium source. [f] [{Rh(C$_2$H$_4$)$_2$Cl}$_2$] as rhodium source.

Moreover, the effects of the anion of the silver salts were examined using 0.5 mol% of rhodium (Table 2). The hexafluoroantimonate, hexafluoroarsenate and perchlorate silver salts were less suitable than the tetrafluoroborate salt (Table 2, entries 1–3), and the hexafluorophosphate, trifluoroacetate and triflimide salts afforded slightly lower levels of selectivity than AgBF$_4$ (compare Table 2, entries 4–6 versus Table 1, entry 5). In the presence of 0.5 mol% of rhodium, AgOTf appeared to be superior to AgBF$_4$, but when the amount of rhodium was increased to 1 mol%, AgBF$_4$ again performed better (compare Table 2, entries 7 and 8 versus Table 1, entries 3 and 5).

Table 2. Screening of various silver salts.

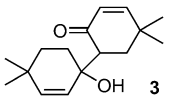


1b 2b

Entry	Additive	Conv [%][a]	Yield [%][a]	*ee* [%][a]
1	$AgSbF_6$	54	20	86
2	$AgAsF_6$	45	17	83
3	$AgClO_4$	44	24	68
4	$AgPF_6$	84±2	49±7	90±2
5	AgO_2CCF_3	49±6	33±6	91±1
6	$AgNTf_2$	58±1	36±3	89±2
7	AgOTf	56±3	48±7	92±2
8[b]	AgOTf	82±2	79±2	97±1

[a] Determined by GC. Values with standard deviation represent the mean of 3 experiments. [b] With 0.5 mol% [{Rh(cod)Cl}$_2$], 1.2 mol% (*R*)-binap, and 1.5 mol% AgOTf.

Notably, GC analysis of these reactions never indicated complete conversion, regardless of the reaction time, even if NMR analysis of the crude products after an aqueous workup showed no remaining enone **1b**. These contradictory observations are due to formation of dimeric compound **3** (in yields below 5%), which undergoes a retro-aldol reaction to form enone **1b** in the GC injector (Figure 1).



3

Figure 1. Side product **3** formed during the synthesis of compound **2b**.

The results of the catalyst optimisation experiments, described above, suggest that the catalytic system is rather sensitive towards the presence of cycloocta-1,5-diene (cod). The best results are achieved with a 1:1 ratio of diene and rhodium (Table 1, entry 3), but both a 2:1 ratio (Table 1, entry 8) or the complete absence of cod (Table 1, entry 9) is unfavourable. Moreover, the transformation is not as successful when extra cod is added.[13]

Inspection of the catalyst mixture used for Table 1, entry 3 by ^{31}P NMR spectroscopy revealed the presence of [Rh(binap)(cod)]BF_4 as the main compound prior to addition of the enone and $AlMe_3$.[14] Upon addition of $AlMe_3$, the reaction mixture immediately turned black, thus indicating the formation of elemental silver; independent treatment of a suspension of AgCl in THF with $AlMe_3$ led to the same black precipitate. The presence of ethane and $AlMe_2Cl$ was proven by GC-MS analysis of the gas phase and ^{1}H NMR analysis of the liquid phase, respectively [Eq. (1)].

$$AgCl + AlMe_3 \xrightarrow{THF} Ag + AlMe_2Cl + 1/2\ C_2H_6 \quad (1)$$

The picture becomes rather puzzling because $AlMe_2Cl$ rapidly reacts with the monomeric rhodium complex. This reaction leads to formation of the chloride-bridged dimeric precatalyst, as observed by ^{31}P NMR spectroscopy, and, presumably, also a cationic aluminium species[15] [Eq. (2) and (3)].

$$[Rh(cod)_2]BF_4 + binap \xrightarrow[-\ cod]{THF} [Rh(binap)(cod)]BF_4 \quad (2)$$

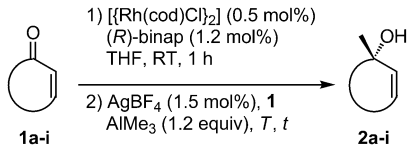
$$[Rh(binap)(cod)]BF_4 + AlMe_2Cl \xrightarrow[-\ cod]{} 1/2\ [\{Rh(binap)Cl\}_2] + "AlMe_2BF_4" \quad (3)$$

Therefore, some amount of the precipitated chloride obviously becomes available upon addition of $AlMe_3$. If the solid AgCl was removed by filtration prior to addition of the alane, the resulting catalyst was less selective.[16,17] Similarly to the effect of the cod ligand, there is obviously a subtle effect of the chloride on the reaction. On the one hand, it slows down formation of the reactive catalyst species; on the other hand, it may stabilize the catalyst against decomposition.

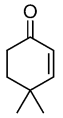
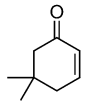
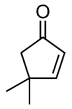
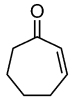
Using the optimised reaction conditions, various cycloalk-2-enones with 5–7-membered rings were converted into the corresponding tertiary allylic alcohols, all with $\geq$ 95% *ee* (Table 3). The yields achieved when 0.5 mol% of the dimeric [{Rh(cod)Cl}$_2$] precursor and 1.5 mol% of $AgBF_4$ were used compare very well to yields previously obtained with 2.5 mol% of [{Rh(cod)OMe}$_2$] in the absence of silver salts.[6] When 6-membered rings are used as substrates yields are generally $\geq$ 80%, with the single exception of a substrate with geminal disubstitution at the C5 position (Table 3, entry 3). Also, the method described does not tolerate substituents at the C2 or C3 positions. Cyclopentenones, which were so far unsuitable substrates, now furnish synthetically useful yields of 37–58%, but still require a higher catalyst loading (Table 3, entries 6–8). A good yield was also achieved with cyclohept-2-enone (**1i**, Table 3, entry 9).[18]

The utility of cyclic tertiary allylic alcohols **2** is demonstrated with a formal total synthesis of (−)-frontalin (**6**, Scheme 2), which is the aggregation pheromone of the bark beetle[19] and the male sex pheromone of *Elephas maximus*, the Asian elephant.[20] More than 30 syntheses of enantioenriched frontalin have been performed and in 1998 Mori et al. reported an outstanding large-scale approach delivering 10 g of this compound with 89% *ee* in 7.8% yield over 10 steps.[21] The acetonide-protected triol **5** is a key intermediate and is obtained in six steps in Mori's synthesis.[22] Starting with an asymmetric 1,2-addition to cyclohex-2-enone (**1a**), protected triol **5** is now available in 3 steps by ozonolysis of compound **2a** with a reductive workup, followed by protection of the 1,2-diol moiety. Based on the subsequent transformations by Mori et al., this new approach represents a formal total synthesis of (−)-frontalin (**6**) in 19% yield over 7 steps with 99% *ee*.[23] Thus, a significant improvement was achieved that is noteworthy because of the increasing use of frontalin for the regulation of beetle populations,[24] and because of the observation that only the (−)-enantiomer is bioactive.[21]

Table 3. Asymmetric 1,2-addition to cycloalkenones.

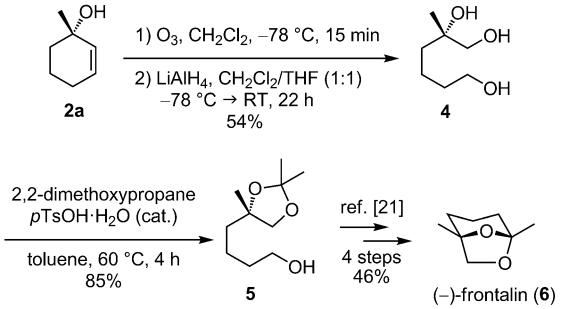


1a-i 2a-i

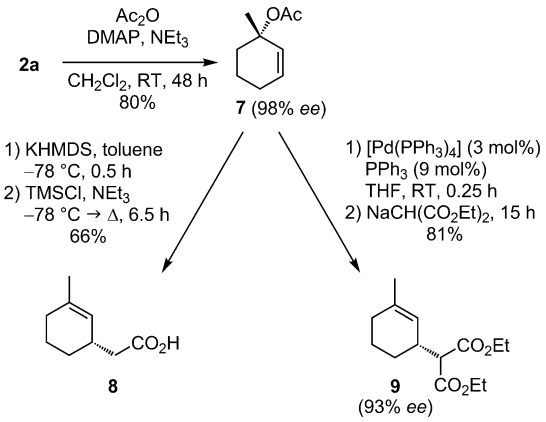
Entry	Enone	*T* [°C]	*t* [h]	Yield [%][a]	*ee* [%][b]
1	 **1a**	RT	0.5	88(84)	99
2	 **1b**	60	2	85(86)	97
3	 **1c**	RT	3	34(31)	98
4[c]	 **1d**	RT	1	83	>99
5	 **1e**	0	2.5	90	>99
6[d]	 **1f**	RT	2	37(10)	95
7[e]	 **1g**	40	4	58(28)	95
8	 **1h**	RT	2	45	99
9	 **1i**	RT	2	72(74)	99

[a] Isolated yield. Values in parentheses with 2.5 mol% [{Rh(cod)OMe}$_2$] without $AgBF_4$.[6] [b] Determined by GC. [c] (*S*)-binap was used to form the *cis*-configured product as a single diastereomer (matched pair, compare ref. [10]). [d] With 2.5 mol% [{Rh(cod)Cl}$_2$], 6.0 mol% (*R*)-binap, and 7.5 mol% $AgBF_4$. [e] With 1.0 mol% [{Rh(cod)Cl}$_2$], 2.4 mol% (*R*)-binap, and 3.0 mol% $AgBF_4$.

Besides oxidative degradation of the C=C bonds, cyclic allylic alcohols **2** are well-suited for sigmatropic rearrangements that proceed with the transfer of chirality. Overman and Mislow–Evans rearrangements furnishing allylic amines and sulfoxides, respectively, have already been reported with cyclic allylic alcohol substrates.[25] We decided to pursue a Claisen rearrangement. At first, the Johnson protocol, that is, treatment with triethyl orthoacetate in the presence of propionic acid, was attempted; however, unsatisfying results were achieved. This might be caused by the acidic conditions, which favour dehydration of the starting material. In contrast, the Ireland protocol proceeds under alkaline conditions. For this transformation, allylic alcohol **2a** was acetylated with Ac_2O to afford compound **7** in 80% yield (Scheme 3).[26] Formation of the respective trimethylsilyl enol ether at −78°C, [3,3]-sigmatropic rearrangement in refluxing toluene and hydrolysis of the initially formed silyl ester furnished desired carboxylic acid **8** in 66% yield.[27] Compound **8** is a versatile chiral building block and racemic derivatives have previously been prepared either by related rearrangements[28a,b] or by a Tsuji–Trost reaction that starts from diethyl malonate and 3-methylcyclohex-2-enyl acetate (the regioisomer of compound **7**).[28c] To prove chirality transfer, acetate **7** (98% *ee*) was similarly transformed, the product **9** being obtained in 81% yield with 93% *ee* (Scheme 3). Thus, transition-metal-catalysed allylic substitu-



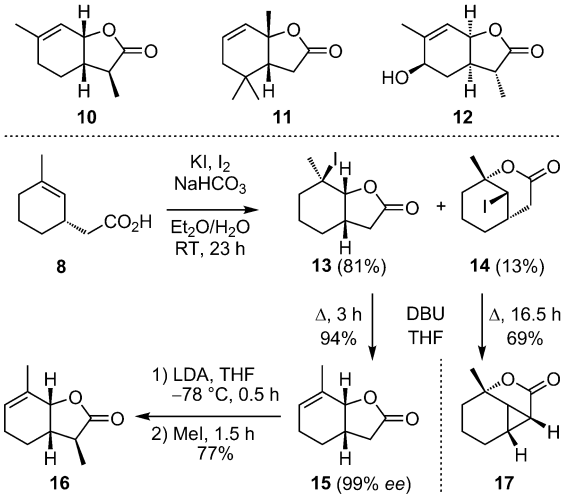
Scheme 2. Formal total synthesis of (−)-frontalin (**6**).



Scheme 3. Claisen rearrangement and Tsuji–Trost reaction of acetate **7** (DMAP = 4-dimethylaminopyridine; KHMDS = potassium hexamethyl disilazide; TMSCl = trimethylsilyl chloride).

tions represent further useful applications of allylic alcohols **2**.[29]

Carboxylic acid **8** is suitable for cyclization to form the core structure of bicyclic lactones, which frequently occur either as natural products themselves or as intermediates in natural product syntheses (Scheme 4). The famous "wine



Scheme 4. Synthesis of bi- and tricyclic lactones (DBU = 1,8-diazabicyclo-[5.4.0]undec-7-ene; LDA = lithium diisopropylamide).

lactone" (**10**) is a flavour component with an odour threshold of only 0.01–0.04 pg L^{-1}[30a] that has been isolated from Koala urine,[30b] but is also found in wine[30c] black pepper,[30d] and fruit juices.[30e] In addition, lactone **11** is an intermediate in the syntheses of (*S*)-actinidiolide and epiloliolide by Mori et al.;[31] a synthesis of paeonilactone A by Bäckvall et al. involved lactone **12**.[32] In a similar way to the preparation of compound **10** by Helmchen et al. and Bartlett et al.,[33] compound **8** was transformed in an iodolactonisation. Interestingly, this reaction proceeded with 6:1 regioselectivity furnishing iodolactones **13** and **14**. Major product **13** was subjected to an elimination reaction, furnishing the unsaturated lactone **15**; the structure of **15** was proven by X-ray analysis.[34] In addition, determination of the *ee* value showed that no racemisation took place along the reaction sequence starting from alcohol **2a**. To finish the preparation of an isomer of wine lactone **10**, a diastereoselective methylation was performed, compound **16** being obtained in 77% yield. Finally, the structure of minor product **14** from the iodolactonisation was also proven by X-ray analysis;[34] under the reaction conditions of the elimination, iodolactone **14** was transformed into the tricyclic lactone **17** in an intramolecular alkylation that led to a 3-*exo*-tet cyclisation.[35]

Conclusion

In summary, preliminary ^{31}P NMR analysis of the Rh^{I}/binap-catalysed 1,2-addition of $AlMe_3$ to enones allowed for the development of an improved catalytic system. Careful optimisation indicated a significant influence of the amount of cod used and pointed to a subtle effect of the content of chloride in the reaction mixture. This unique enantioselective 1,2-addition of methyl groups to cyclic enones furnishes high yields of products with just 1 mol% of rhodium catalyst and is applicable to various unsubstituted, as well as, substituted cycloalkenones. The only restriction appears to be that the substrate must not contain a substituent at the C2 or C3 positions. On the basis of the synthetic applications in this report, the resulting allylic alcohols are highly versatile synthons, especially because oxidative cleavage of the C=C bond provides access to acyclic scaffolds. Currently, advanced NMR studies are being performed together with collaboration partners to get a better understanding of the reaction mechanism. This understanding might help to further increase the substrate scope towards acyclic enones or cycloalkenones with tri- or even tetrasubstituted C=C bonds.

Experimental Section

General: ^{1}H NMR spectra were recorded at 300 MHz on a Bruker AV-300 or at 500 MHz on a Bruker DRX 500 spectrometer. Chemical shifts are reported as δ values relative to the residual proton signal ($CHCl_3$: $\delta = 7.26$ ppm, $[D_5]$DMSO: 2.50 ppm) as an internal reference. ^{13}C NMR spectra were recorded at 125 MHz on a Bruker DRX 500, at 75.5 MHz on a Bruker AV-300 or at 62.5 MHz on a Bruker DPX 250 spectrometer. Chemical shifts are reported as δ values relative to $CDCl_3$ ($\delta =$ 77.16 ppm) or $[D_6]$DMSO ($\delta = 39.52$ ppm). ^{31}P NMR spectra were recorded at 101 MHz on a Bruker DPX 250 spectrometer. Chemical shifts are reported as δ values relative to H_3PO_4 as internal reference ($\delta =$ 0.00 ppm). IR spectra were recorded on a Bruker Alpha-P FT-IR spectrometer. Electrospray ionisation (ESI) mass spectra were recorded on a Finnigan LTQ FT spectrometer by the analytical service department of the Philipps-Universität Marburg. Optical rotations were measured on a Perkin–Elmer 241 polarimeter with concentrations in g/100 mL. Melting points are uncorrected. Gas chromatograms were recorded with a Shimadzu GC-2010 Plus with an AOC-20i autosampler. GC yields were determined on a Supelco SPB-1 column (30 m, 0.32 mm internal diameter, 0.25 μm film) against mesitylene as internal standard; *ee* values were determined on a Chiral-Separations Cyclodextrin TA (6-TBDMS-2,3-acetyl-β-cyclodextrin, 50% in PS086, 25 m, 0.25 mm internal diameter, 0.125 μm film) or a Cyclodextrin TE (6-TBDMS-2,3-ethyl-β-cyclodextrin, 30% in PS086, 30 m, 0.25 mm internal diameter, 0.125 μm film) column. Helium was used as carrier gas and temperature programs are given with the respective substances. Column chromatography was carried out on MN Kieselgel 60 M (Machery–Nagel, 0.04–0.063 mm). TLC analysis was carried out on precoated sheets (Merck DC Kieselgel 60 F254). Medium-pressure liquid chromatography (MPLC) was carried out on Interchim puriFlash SI-HP columns. Solvents used for extraction and chromatography were of technical grade and distilled prior to use. All moisture-sensitive reactions were carried out under dry nitrogen or argon in oven- or flame-dried glassware. THF and toluene were distilled from sodium benzophenone ketyl, dichloromethane and triethylamine from CaH_2. Samples of the racemic allylic alcohols for GC analysis were prepared by MeLi addition to the respective enones. Stock solutions of $AlMe_3$ were prepared by dissolving the neat reagent in anhydrous hexane.

(*S*)-1-Methylcyclohex-2-en-1-ol (**2a**): A solution of $[\{Rh(cod)Cl\}_2]$ (2.47 mg, 5.00 μmol) and (*R*)-binap (7.47 mg, 12.0 μmol) in anhydrous THF (2.50 mL) was stirred for 1 h at room temperature. $AgBF_4$ (29.2 μL, 15.0 μmol, 100 mg mL^{-1} in THF) and cyclohex-2-enone (**1a**, 96.8 μL, 96.1 mg, 1.00 mmol) were added, followed by dropwise addition of $AlMe_3$ (235 μL, 1.20 mmol, 5.10 M in hexane). After 0.5 h, the reaction mixture was poured into a stirred mixture of pentane (25 mL) and H_2O

(0.02 mL), and stirring was continued for 15 min. Na_2SO_4 (1.5 g) and charcoal (0.7 g) were added and the crude product was obtained after filtration and careful removal of the solvent under reduced pressure. MPLC (pentane, 4 g silica gel 30 μm) yielded 99 mg (88%) of allylic alcohol **2a** as a colourless oil (R_f=0.33, cyclohexane/EtOAc 2:1). The *ee* value was determined by GC analysis (Cyclodextrin TA; 4 min 60°C isothermal→2 K min^{-1} to 100°C; 45 cm s^{-1} gas flow), retention times: 12.8 min (*S*)-enantiomer, 13.2 min (*R*)-enantiomer, 99% *ee*; the physical and spectroscopic data were consistent with those reported in the literature.[36]

(*S*)-2-Methylhexane-1,2,6-triol (4): (*S*)-1-Methylcyclohex-2-en-1-ol (**2a**, 195 mg, 1.74 mmol) was dissolved in anhydrous CH_2Cl_2 (25 mL), and a stream of ozone in oxygen was passed through the solution at −78°C until a blue colour persisted (15 min). Excess ozone was first displaced with oxygen, then with argon. Anhydrous THF (25 mL) and $LiAlH_4$ (100 mg, 2.64 mmol) were added to the solution, and it was allowed to warm to room temperature. After 22 h, saturated aqueous potassium sodium tartrate (9 mL) was added in portions at 0°C, the mixture was filtered over Celite, and the filtrate concentrated under reduced pressure. Flash chromatography (CH_2Cl_2/MeOH 10:1→7:1) yielded 140 mg (54%) of triol **4** as a highly viscous, colourless oil (R_f=0.14, CH_2Cl_2/MeOH 10:1). $[\alpha]_D^{20}=-2.1$ (c=1.0 in EtOAc); ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ=0.97 (s, 3H), 1.23–1.41 (m, 6H), 3.14 (m, 2H), 3.37 (m, 2H), 3.95 (s, 1H), 4.34 (t, J=5.1 Hz, 1H), 4.44 ppm (t, J=5.7 Hz, 1H); ^{13}C NMR (75.5 MHz, [D$_6$]DMSO): δ=19.7, 24.1, 33.5, 38.4, 60.9, 69.0, 71.5 ppm; HRMS (ESI): m/z calcd for $C_7H_{16}O_3Na$: 171.0992; found: 171.0995.

(*S*)-4-(2,2,4-Trimethyl-1,3-dioxolan-4-yl)butan-1-ol (5): Triol **4** (64.0 mg, 432 μmol), 2,2-dimethoxypropane (52.9 μL, 45.0 mg, 432 μmol), and *p*TsOH·H$_2$O (4.11 mg, 21.6 μmol) were dissolved in anhydrous toluene (7.0 mL) and stirred for 4 h at 60°C. The mixture was then concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 1:1) yielded 69 mg (85%) of dioxolane **5** as a colourless oil (R_f=0.20, cyclohexane/EtOAc 1:1). $[\alpha]_D^{19}=-2.6$ (c=1.0 in $CHCl_3$); HRMS (ESI): m/z calcd for $C_{10}H_{20}O_3Na$: 211.1305; found: 211.1304; The NMR spectroscopic data were consistent with those reported in the literature.[22a]

(*S*)-1-Methylcyclohex-2-enyl acetate (7): (*S*)-1-Methylcyclohex-2-en-1-ol (**2a**, 112 mg, 1.00 mmol), triethylamine (282 μL, 205 mg, 2.00 mmol), acetic anhydride (190 μL, 205 mg, 2.02 mmol), and 4-dimethylaminopyridine (12.2 mg, 100 μmol) were stirred in CH_2Cl_2 (2.0 mL) at room temperature for 48 h. The mixture was diluted with CH_2Cl_2 (70 mL) and washed with $KHSO_4$ (15 mL, 10% aq), $NaHCO_3$ (10 mL, saturated aq) and water (2×10 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. Distillation (room temperature, 7.8×10^{-2} mbar) yielded 124 mg (80%) of **7** as a colourless oil. The *ee* value was determined by GC analysis (Cyclodextrin TA; 4 min 60°C isothermal→2 K min^{-1} to 100°C; 45 cm s^{-1} gas flow), retention times: 9.4 min (*S*)-enantiomer, 9.9 min (*R*)-enantiomer, 98% *ee*; $[\alpha]_D^{22}=-167.5$ (c=1.0 in CH_2Cl_2); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.53 (s, 3H), 1.57–1.81 (m, 3H), 1.88–2.12 (m, 3H), 1.97 (s, 3H), 5.78–5.84 (m, 1H), 6.03–6.08 ppm (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=18.9, 22.5, 25.0, 26.1, 35.7, 78.7, 130.4, 130.5, 170.6 ppm; IR: $\tilde{\nu}$=3034, 2937, 2872, 2837, 1728 (s), 1439, 1367, 1242 (s), 1200, 1172, 1144, 1091, 1018, 967, 940, 913, 874, 841, 813, 732, 684, 609, 502, 471 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{14}O_2Na$: 177.0886; found 177.0883.

(*S*)-2-(3-Methylcyclohex-2-enyl)acetic acid (8): At −78°C a solution of **7** (841 mg, 5.45 mmol) in toluene (15 mL) was added dropwise to a solution of potassium hexamethyldisilazide (9.89 mL, 6.55 mmol, 15% in toluene) in toluene (10 mL). After 30 min at this temperature, a solution of trimethylsilyl chloride (1.11 mL, 950 mg, 8.75 mmol) and triethylamine (1.21 mL, 880 mg, 8.70 mmol) in toluene (15 mL) was added dropwise. The cooling bath was removed after 30 min, and the mixture was stirred for 1 h at room temperature and for 5 h under reflux. After cooling, the mixture was poured into aqueous NaOH (20 mL, 2 N) and stirred for 15 min, followed by dilution with Et_2O (40 mL) and extraction with aqueous NaOH (3×40 mL, 2 N). The combined aqueous phases were acidified to pH 2 with hydrochloric acid (6 M) and extracted with Et_2O (3×150 mL). Drying (Na_2SO_4) and evaporation of the solvent followed by flash chromatography (cyclohexane/EtOAc 1:1) yielded 557 mg (66%) of compound **8** as a yellow oil (R_f=0.58). $[\alpha]_D^{22}=+38.8$ (c=1.0 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.16–1.27 (m, 1H), 1.49–1.60 (m, 1H), 1.65 (d, J=0.6 Hz, 3H), 1.68–1.93 (m, 4H), 2.23–2.38 (m, 2H), 2.56 (m, 1H), 5.28 (br s, 1H), 10.34 ppm (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=21.5, 24.0, 28.8, 30.1, 32.5, 41.0, 124.1, 135.8, 179.4 ppm; IR: $\tilde{\nu}$=2923 (br), 2861, 2671, 1702 (s), 1409, 1338, 1288, 1205, 935, 856, 810, 694, 635, 445, 411 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{13}O_2$: 153.0921; found 153.0924.

Diethyl (*R*)-2-(3-methylcyclohex-2-en-1-yl)malonate (9): Sodium hydride (49.9 mg, 2.08 mmol) was added at room temperature to a solution of diethyl malonate (346 μL, 363 mg, 2.27 mmol) in THF (4.0 mL) and stirred for 15 min. In a separate flask, compound **7** (100 mg, 648 μmol), [Pd(PPh$_3$)$_4$] (22.5 mg, 19.5 μmol) and triphenylphosphine (15.3 mg, 58.3 μmol) were dissolved in THF (1.0 mL) and stirred for 15 min. Afterwards, the solution of sodium malonate was added, and the mixture was stirred for an additional 15 h. This solution was then poured into Et_2O (20 mL) and water (10 mL) and the aqueous phase was extracted with Et_2O (2×10 mL). The organic phases were dried over $MgSO_4$ and the solvent was removed under reduced pressure. Flash chromatography (hexane/EtOAc 15:1) yielded 134 mg (81%) of malonate **9** as a colourless oil (R_f=0.28). The *ee* value was determined by GC analysis (Cyclodextrin TE; 4 min 60°C isothermal→1 K min^{-1} to 100°C→20 K min^{-1} to 160°C→10 min isothermal; 45 cm s^{-1} gas flow), retention times: 50.4 min (*S*)-enantiomer, 50.6 min (*R*)-enantiomer, 93% *ee*; $[\alpha]_D^{24}=+19$ (c=1.3 in EtOAc); ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.25–1.33 (m, 1H), 1.26 (t, J=7.1 Hz, 3H), 1.27 (t, J=7.1 Hz, 3H), 1.51–1.60 (m, 1H), 1.64 (s, 3H), 1.69–1.76 (m, 2H), 1.83–1.96 (m, 2H), 2.87 (m, 1H), 3.20 (d, J=9.6 Hz, 1H), 4.16–4.24 (m, 4H), 5.25 ppm (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ=14.3 (2C), 21.4, 24.1, 26.6, 30.0, 35.7, 57.6, 61.3 (2C), 121.9, 136.8, 168.75, 168.81 ppm; IR: $\tilde{\nu}$=2931, 2866, 1734 (s), 1451, 1371, 1331, 1295, 1257, 1150, 1033, 862, 810 cm^{-1}; HRMS (ESI): m/z calcd for $C_{14}H_{22}O_4H$: 255.1591; found 255.1593; m/z calcd for $C_{14}H_{22}O_4Na$: 277.1410; found 277.1412.

(3a*S*,7*R*,7a*R*)-7-Iodo-7-methylhexahydrobenzofuran-2(3*H*)-one (13) and **(1*S*,5*S*,9*S*)-9-Iodo-1-methyl-2-oxabicyclo[3.3.1]nonan-3-one (14)**: A solution of compound **8** (427 mg, 2.77 mmol) in Et_2O (9.5 mL) and aqueous $NaHCO_3$ (9.4 mL, 4.7 mmol, 0.50 N) was stirred at room temperature for 20 min. Then, a solution of potassium iodide (2.75 g, 16.6 mmol) and iodine (1.40 g, 5.52 mmol) in H_2O (11.0 mL) was added and the reaction mixture was stirred for 23 h. Saturated aqueous $Na_2S_2O_3$ was added until a clear solution was obtained. The mixture was then extracted with Et_2O (4×30 mL). The combined organic phases were washed with saturated aqueous $NaHCO_3$ (100 mL) and brine (100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 1:1) yielded 626 mg (81%) of lactone **13** (R_f=0.61, cyclohexane/EtOAc 2:1) and 104 mg (13%) of lactone **14** (R_f=0.53, cyclohexane/EtOAc 2:1) as colourless solids. Lactone **13**: Mp: 61–62°C; $[\alpha]_D^{22}=-75.8$ (c=1.0 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.99–1.27 (m, 2H), 1.72–1.84 (m, 3H), 1.95–2.06 (m, 1H), 2.24 (d, J=18.0 Hz, 1H), 2.25 (s, 3H), 2.69 (dd, J=16.7, 6.3 Hz, 1H), 2.86–2.95 (m, 1H), 4.68 ppm (d, J=3.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=23.6, 26.6, 33.8, 34.8, 38.0, 39.2, 52.0, 86.0, 176.4 ppm; IR: $\tilde{\nu}$=2938, 2865, 1768 (s), 1447, 1419, 1374, 1320, 1288, 1221, 1177, 1143, 1049, 1027, 965, 937, 888, 853, 829, 767, 687, 597, 557, 507, 428 cm^{-1}; HRMS (ESI): calcd for $C_9H_{13}IO_2Na$: 302.9852; found 302.9863. Lactone **14**: Mp: 114–116°C; $[\alpha]_D^{22}=+23.4$ (c=1.0 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.54 (s, 3H), 1.58–1.71 (m, 3H), 1.75–1.86 (m, 1H), 2.13–2.26 (m, 2H), 2.45 (m, 1H), 2.57 (dd, J=18.5, 1.1 Hz, 1H), 2.95 (ddd, J=18.5, 6.8, 1.1 Hz, 1H), 4.44 ppm (m, 1H); ^{13}C NMR (62.5 MHz, $CDCl_3$): δ=17.1, 26.5, 30.5, 32.3, 34.2, 36.4, 37.0, 82.7, 171.1 ppm; IR: $\tilde{\nu}$=2981, 2929, 2866, 1779, 1712 (s), 1444, 1409, 1372, 1336, 1304, 1278, 1228 (s), 1176, 1148, 1109, 1081, 1048, 1016, 966, 946, 897, 819, 666, 571, 544, 517, 493, 435 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{13}IO_2Na$: 302.9852; found 302.9862; Crystals suitable for X-ray analysis were obtained by slow evaporation from pentane.

(3a*S*,7a*R*)-7-Methyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one (15): A solution of compound **13** (626 mg, 2.23 mmol) and 1,8-diazabicyclo-[5.4.0]undec-7-ene (400 μL, 408 mg, 2.68 mmol) in THF (7 mL) was stirred under reflux for 3 h. After cooling, the mixture was diluted with

EtOAc, Et_2O and H_2O (10 mL each). The aqueous phase was acidified to pH 2 with hydrochloric acid (6 M) and extracted with Et_2O (3×30 mL). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 5:1) yielded 320 mg (94%) of lactone **15** as an off-white solid (R_f=0.36, cyclohexane/EtOAc 2:1). The *ee* value was determined by GC analysis (Cyclodextrin TE; 4 min 60 °C isothermal→2 K min^{-1} to 100 °C→20 K min^{-1} to 160 °C→5 min isothermal; 45 cm s^{-1} gas flow), retention times: 28.6 min (3a*S*,7a*R*)-enantiomer, 29.0 min (3a*R*,7a*S*)-enantiomer, 99% *ee*; mp: 55 °C; $[\alpha]_D^{22}=+23.7$ (c=1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ= 1.35–1.48 (m, 1H), 1.65–1.74 (m, 1H), 1.82 (d, J=1.6 Hz, 3H), 1.93–2.17 (m, 2H), 2.33 (dd, J=17.2, 3.4 Hz, 1H), 2.50–2.61 (m, 1H), 2.74 (dd, J= 17.2, 8.1 Hz, 1H), 4.62 (d, J=5.9 Hz, 1H), 5.78 ppm (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=20.8, 23.2, 23.9, 34.1, 35.3, 79.5, 128.4, 130.3, 176.7 ppm; IR: $\tilde{\nu}$=2950, 2916, 2851, 1750 (s), 1446, 1409, 1381, 1333, 1291, 1249, 1229, 1201, 1167 (s), 1089, 1071, 1023, 974, 932, 873, 828, 792, 694, 617, 547, 495, 443, 418 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{12}O_2Na$: 175.0730; found 175.0729; crystals suitable for X-ray analysis were obtained by slow evaporation from pentane/Et_2O.

(3*S*,3a*S*,7a*R*)-3,7-Dimethyl-3,3a,4,5-tetrahydrobenzofuran-2(7a*H*)-one (16): A solution of lactone **15** (130 mg, 854 μmol) in THF (3.0 mL) was slowly added to a solution of lithium diisopropylamide (LDA) (3.51 mL, 926 μmol, 0.264 M in THF) at −78 °C and stirred for 30 min. Methyl iodide (304 μL, 693 mg, 4.88 mmol) was added and the mixture was stirred for another 1.5 h. After addition of saturated aq NH_4Cl (7.5 mL) the reaction mixture was warmed to room temperature and extracted with Et_2O (3×10 mL). The combined organic phases were dried (Na_2SO_4) and concentrated under reduced pressure. Flash chromatography (CH_2Cl_2) yielded 109 mg (77%) of **16** as a colourless oil (R_f=0.42) that solidified in the freezer (−28 °C). $[\alpha]_D^{24}=-38.5$ (c=1.0 in EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.27 (d, J=7.1 Hz, 3H), 1.61–1.83 (m, 2H), 1.78 (d, J=1.7 Hz, 3H), 2.00–2.09 (m, 2H), 2.28–2.49 (m, 2H), 4.72 (d, J=6.8 Hz, 1H), 5.67 ppm (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$): δ=14.2, 20.3, 21.5, 22.3, 37.6, 41.7, 78.0, 127.1, 131.3, 179.8 ppm; IR: $\tilde{\nu}$= 2970, 2926, 1764 (s), 1449, 1380, 1328, 1198, 1164, 1083, 1029, 986, 957, 918, 892, 808, 592, 564, 503 cm^{-1}; HRMS (ESI): m/z calcd for $C_{10}H_{14}O_2Na$: 189.0886; found 189.0887.

(2a*R*,2a*S*,2b*R*,5a*S*)-5a-Methylhexahydrocyclopropa[*cd*]benzofuran-2-(2a*H*)-one (17): A solution of **14** (104 mg, 371 μmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (66.8 μL, 68.1 mg, 448 μmol) in THF (3.0 mL) was stirred under reflux for 16.5 h. After cooling, the mixture was diluted with EtOAc and H_2O (20 mL each). The aqueous phase was acidified to pH 2 with hydrochloric acid (6 M) and extracted with Et_2O (3×40 mL). The combined organic phases were dried ($MgSO_4$), and concentrated under reduced pressure. Flash chromatography (cyclohexane/EtOAc 5:1) yielded 38.9 mg (69%) of lactone **17** as a colourless oil (R_f= 0.39, cyclohexane/EtOAc 2:1). $[\alpha]_D^{26}=+24.0$ (c=0.45 in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): δ=1.43–1.61 (m, 4H), 1.53 (s, 3H), 1.72–1.77 (m, 1H), 1.80–1.85 (m, 1H), 1.94–2.01 (m, 1H), 2.10 ppm (d, J= 8.4 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ=16.4, 18.3, 20.0, 25.3, 27.9, 28.6, 31.9, 80.9, 175.2 ppm; IR: $\tilde{\nu}$=2933, 2876, 1748 (s), 1454, 1379, 1354, 1326, 1288, 1255, 1218, 1185, 1156, 1119, 1022, 982, 946, 906, 823, 755, 654, 529, 504, 452 cm^{-1}; HRMS (ESI): m/z calcd for $C_9H_{13}O_2$: 153.0910; found 153.0907; m/z calcd for $C_9H_{12}O_2Na$: 175.0730; found 175.0726.

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