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# Novel Enantioselective Sequentially Rhodium(I)/BINAP-Catalyzed Cycloisomerization–Hydrogenation–Isomerization–Acetalization (CIHIA)

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**Abstract:** Linear, easily accessible alkyl and (hetero)aryl-substituted alkynyl allyl alcohols are readily and enantioselectively transformed into 2,7-dioxabicyclo[3.2.1]octanes by a sequential rhodium-catalyzed process. Based on the initial cycloisomerization, the *in situ* generated rhodium(I)-BINAP complex enables a subsequent reduction with hydrogen and the transformation into bicyclic frameworks.

**Keywords:** asymmetric catalysis; cyclization; homogeneous catalysis; hydrogenation; rhodium

## Introduction

Highly selective methodologies for transformations of linear precursors into hetero- and carbocyclic structures represent a maximum gain in molecular complexity. The advent of transition metal-catalyzed processes was of paramount benefit and has revolutionized the field of organic syntheses giving access to novel economically and ecologically benign processes. In particular, the use of one catalyst for more than one type of transformation in a one-pot fashion, generally referred to as sequential catalysis,[1] has emerged as a powerful method by catching two or even more birds with one stone.

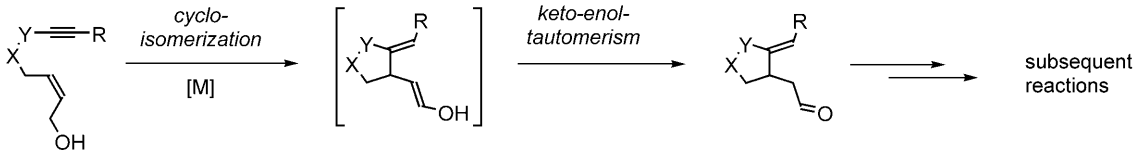
Among the numerous catalytic carbon-carbon bond-forming processes as well as enyne cyclization and especially cycloisomerization,[2] the intramolecular and transition metal catalyzed-version of the Alder-ene reaction,[3] has become an outstanding tool to form cycles bearing a diene functionality.

In particular, rhodium(I)-catalyzed cycloisomerization processes,[4] firstly published by Zhang,[5] have taken pride of place to generate a tetrahedral stereogenic center from a planar $sp^2$-carbon in the starting material in a highly effective and selective manner. The transformation of 1,6-enynes by a cationic rhodium complex coordinated to enantiomerically pure chelating bisphosphane ligands led to the formation of five-membered rings.[6] Further ligand screenings proved the superior role of the rhodium-BINAP system.[7] Additionally, the configuration of the new stereogenic center was determined by anomalous diffraction in the X-ray crystal structure analysis[8] and indirectly by diastereoselective kinetic resolution.[9]

In the case of cycloisomerization reactions with alkynyl allyl alcohols, a reactive aldehyde functionality is generated by virtue of the tautomerism of the dienol intermediate. These resulting enals set the stage for consecutive transformations, particularly in sequentially catalyzed one-pot processes (Scheme 1).

As part of our program to design new transition metal-catalyzed sequences initiated by intramolecular cycloisomerization,[10] we are particularly interested in sequential metal-catalyzed one-pot processes. Within our studies dealing with the scope and limitations of different transition metal catalysts, the palladium-catalyzed cycloisomerization works very well for the TMS-substituted alkynic allyl alcohols and was already successfully applied in cycloisomerization–Wittig,[10a] cycloisomerization–Leuckart–Wallach[10b] and cycloisomerization–Knoevenagel[10c] sequences in a one-pot fashion. Notably, two sequential palladium-catalyzed processes were combined in a cycloisomerization–reductive amination sequence.[10d] Moreover




**Scheme 1.** Transition metal-catalyzed cycloisomerization as entry to sequential transformations.

the iridium-catalyzed version with aryl-substituted alkynic allyl alcohols led to an interesting, as well twofold iridium-catalyzed, cycloisomerization–Murahashi sequence under very mild reaction conditions.[11]

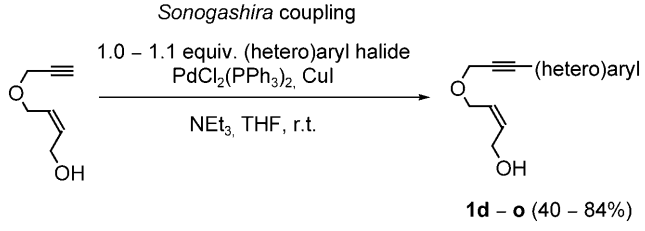
In spite of its great potential, the rhodium-catalyzed cycloisomerization has not been investigated within sequential transformations exploiting the cationic rhodium(I)/BINAP complex for a consecutive reaction step. As rhodium has gained a superior role in catalytic hydrogenation reactions,[12] a sequential hydrogenation step represents an interesting target.

Here we report on the rhodium-catalyzed intramolecular cycloisomerization of alkynyl allyl alcohols to the corresponding enals and its elaboration into a novel cycloisomerization–hydrogenation–isomerization–acetalization (CIHIA) sequence giving access to enantioselective 2,7-dioxabicyclo[3.2.1]octanes in a one-pot fashion.

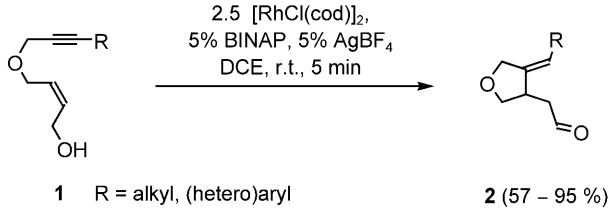
## Results and Discussion

The required linear allenyl substituted (*Z*)-alkynyl allyl alcohol substrates **1a** and **1c** were obtained by simple Williamson etherification of but-2-ene-1,4-diol and 1-bromobut-2-yne or 3-bromoprop-1-ynylbenzene, respectively, in good yields (55% and 85%). The (hetero)aryl-substituted alkynyl allyl alcohol substrates **1d–o** were generated by Sonogashira coupling reactions of (*Z*)-4-(prop-2-ynyloxy)but-2-en-1-ol and the corresponding aryl halide in moderate to good yields (40–84%, Scheme 2, Table 1).

For the rhodium-catalyzed cycloisomerization we first adopted the established reaction parameters by Zhang and Hashmi applying 5% of the $[RhCl(cod)]_2$ precursor, 10% (*rac*)-BINAP and 10% of silver tetrafluoroborate in dichloroethane (DCE) at room temperature. Despite preceding publications, we succeeded in reducing the amount of catalyst to 1.0–2.5% $[RhCl(cod)]_2$ whereas the reactions still proceeded within 5 min at room temperature (Scheme 3, Table 2).




**Scheme 2.** Sonogashira-coupling for the syntheses of the (hetero)aryl substituted alkynyl allyl alcohols **1d–o**.



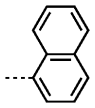
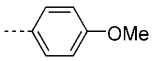
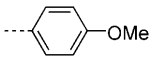
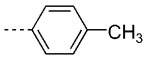
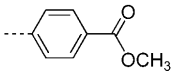
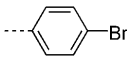
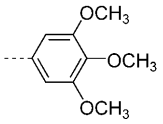
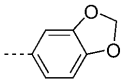
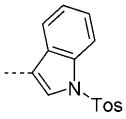

**Scheme 3.** Rhodium(I)/BINAP-catalyzed cycloisomerization of alkyl- and (hetero)aryl-substituted alkyne allyl alcohols **1** to $\gamma,\delta$-enals **2**.

Subjecting **1c** to 5 mol% of $[RhCl(cod)]_2$, 10% BINAP and 10% $AgBF_4$ the cyclization product **2c** was readily propared in a satisfying 78% yield (Table 2, entry 1). Halving the catalyst amount showed no effect on the isolated yield (Table 2, entry 2), and it even increased on going down to 1% of the rhodium dimer (Table 2, entry 3). However, the higher yield does certainly not represent a higher conversion but rather an advancement in the practical isolation of the sensitive aliphatic aldehydes. With the *p*-anisyl substituted **1e** the same parameter changes furnished a stepwise reduced yield of **2e** (Table 2, entries 4–6), whereas in all three cases the TLC control displayed full conversion after 5 min reaction time. The transformations of **1j** proceeded with comparable isolated yield for both 2.5% and 1.0% rhodium dimer (Table 2, entries 7 and 8). In case of the heteroaryl alkynyl allyl alcohol **1o** a satisfying 85% yield was maintained under the established conditions (Table 2, entry 9), but with the low catalyst loading we observed a significantly lower conversion (Table 2, entries 10 and 11). In order to fall short of the rhodium catalyst potential, we have chosen a general catalyst loading of 2.5% $[RhCl(cod)]_2$ dimer for the subsequent cycloisomerization, although we proved sufficient conversion with even lower amounts of catalyst.

Applying the optimized parameters we were able to transform alkyl- as well as (hetero)aryl-substituted alkynyl allyl alcohol substrates **1** to furnish substituted cyclic enals **2** in good to excellent yields (Scheme 3, Table 3). Besides alkyl-substituted alkynyl allyl alcohols (Table 3, entries 1 and 2) also those with elec-

**Table 1.** Sonogashira coupling reactions for the syntheses of the (hetero)aryl substituted alkynyl allyl alcohols **1d–o**.

| Entry | Aryl halide | Product | (Hetero)aryl | Yield [%][a] |
|---|---|---|---|---|
| 1 | 1-Iodonaphthalene | **1d** |  | 60 |
| 2 | 4-Iodoanisole | **1e** |  | 70 |
| 3 | 2-Iodoanisole | **1f** |  | 40 |
| 4 | 4-Iodotoluene | **1g** |  | 66 |
| 5 | Methyl 4-iodobenzoate | **1i** |  | 69 |
| 6 | 1-Bromo-4-iodobenzene | **1j** |  | 73 |
| 7 | 5-Iodo-1,2,3-trimethoxybenzene | **1l** |  | 84 |
| 8 | 5-Iodobenzo[1,3]dioxole | **1m** |  | 53 |
| 9 | 2-Iodothiophene | **1n** |  | 70 |
| 10 | 3-Iodo-1-tosyl-1*H*-indole | **1o** |  | 68 |

[a] Yields refer to isolated yields of compound **1**.

**Table 2.** Different catalyst loads for the cycloisomerization.

| Entry | Alkynyl allyl alcohol **1**, R = | a) $[RhCl(cod)]_2$, b) BINAP, $AgBF_4$ | Product | Yield [%][a] |
|---|---|---|---|---|
| 1 | **1c**, $C_6H_5$ | a) 5%, b) 10% | **2c** | 78 |
| 2 | **1c**, $C_6H_5$ | a) 2.5%, b) 5% | **2c** | 78 |
| 3 | **1c**, $C_6H_5$ | a) 1%, b) 2% | **2c** | 94 |
| 4 | **1e**, 4-$CH_3OC_6H_5$ | a) 5%, b) 10% | **2e** | 88 |
| 5 | **1e**, 4-$CH_3OC_6H_5$ | a) 2. 5%, b) 5% | **2e** | 81 |
| 6 | **1e**, 4-$CH_3OC_6H_5$ | a) 1%, b) 2% | **2e** | 75 |
| 7 | **1j**, 4-$BrC_6H_5$ | a) 2.5%, b) 5% | **2j** | 78 |
| 8 | **1j**, 4-$BrC_6H_5$ | a) 1%, b) 2% | **2j** | 79 |
| 9 | **1o**, 3-$C_{15}H_{13}NO_2S$ | a) 5%, b) 10% | **2o** | 85 |
| 10 | **1o**, 3-$C_{15}H_{13}NO_2S$ | a) 2.5%, b) 5% | **2o** | 77 |
| 11 | **1o**, 3-$C_{15}H_{13}NO_2S$ | a) 1%, b) 2% | **2o** | 54 |

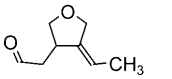
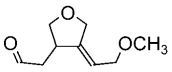
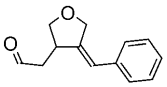
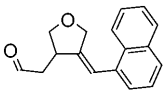
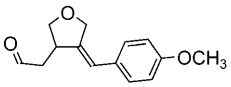
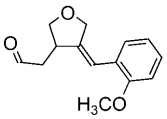
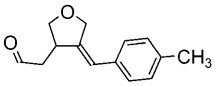
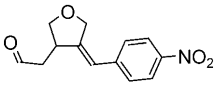
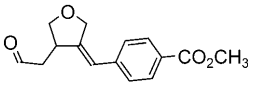
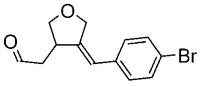
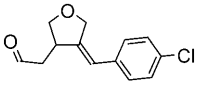
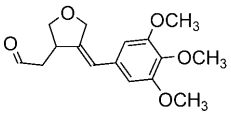
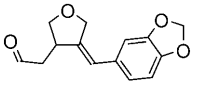
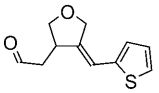
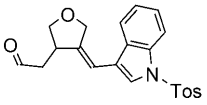
[a] Yields refer to isolated yields of compound **2**.

tronically variable aryl substituents (Table 3, entries 3–13) can be transformed into the expected enals. The substitution pattern plays no limiting role and even heteroaryl-substituted substrates led to the corresponding enals in satisfying yields (Table 3, entries 14 and 15). In contrast to the palladium- and iridium-catalyzed cycloisomerization which both suffer form limitations with respect to the alkyne substituent, the rhodium-catalyzed version enables the transformation of a very broad variety of alkyne substituents. Alkyl as well as aryl substituents qualify for the cyclization reaction.

Notably, for the first time heteroaryl-substituted tetrahydrofuran cores were generated. In addition,

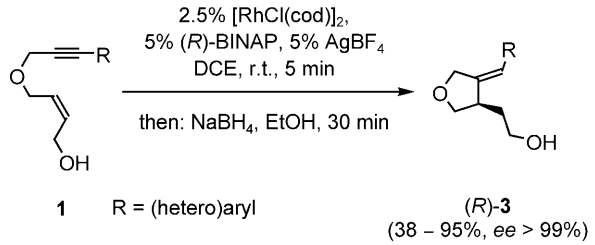
**Table 3.** Cycloisomerization reaction of alkyl and (hetero)aryl substituted alkynyl allyl alcohols **1** to $\gamma,\delta$-enals **2**.[a]

| Entry | Alkynyl allyl alcohol **1**, R = | Product | | Yield [%][b] |
|---|---|---|---|---|
| 1 | **1a**, $CH_3$ |  | **2a** | 93 |
| 2 | **1b**, $CH_2OCH_3$ |  | **2b** | 62 |
| 3 | **1c**, $C_6H_5$ |  | **2c** | 94 |
| 4 | **1d**, 1-naphthyl |  | **2d** | 81 |
| 5 | **1e**, *p*-anisyl |  | **2e** | 88 |
| 6 | **1f**, *o*-anisyl |  | **2f** | 81 |
| 7 | **1g**, *p*-tolyl |  | **2g** | 94 |
| 8 | **1h**, *p*-nitrophenyl |  | **2h** | 89 |
| 9 | **1i**, methyl *p*-benzoate |  | **2i** | 68 |
| 10 | **1j**, *p*-bromophenyl |  | **2j** | 86 |
| 11 | **1k**, *p*-chlorophenyl |  | **2k** | 76 |
| 12 | **1l**, 1,2,3-trimethoxyphen-5-yl |  | **2l** | 73 |
| 13 | **1m**, 1,3-benzodioxol-5-yl |  | **2m** | 67 |
| 14 | **1n**, 2-thienyl |  | **2n** | 95 |
| 15 | **1o**, 3-(*N*-tosyl)indolyl |  | **2o** | 85[c] |

[a] *Reaction conditions:* 1.0 equiv. of alkynyl allyl alcohol **1** (0.2 M in dichloroethane), 0.025 equiv. of $RhCl(cod)]_2$, 0.05 equiv. of BINAP, 0.05 equiv. of $AgBF_4$ solution (0.05 M in dichloroethane).
[b] Yields refer to isolated yields of compound **2**.
[c] 0.05 equiv. of $[RhCl(cod)]_2$, 0.1 equiv. of BINAP, 0.1 equiv. of $AgBF_4$ solution.

the rhodium-catalyzed reaction clearly proves its superior potential with respect to the short reaction times. Elongated reaction times did not result in any consumption of the products. After complete conversion the mixture was stirred for additional 2 h at room temperature as well as heated up to 80 °C for




**Scheme 4.** Cycloisomerization–reduction sequence of (hetero)aryl substituted alkynyl allyl alcohols **1** to 4-arylidenetetrahydrofuran-3-ylethanols **3**.

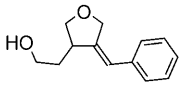
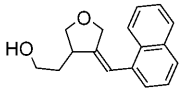
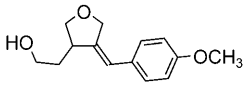
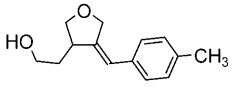
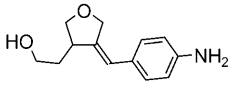
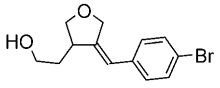
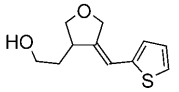
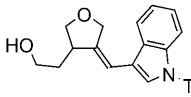
1 h. Neither additional precipitation (besides the initial silver chloride formation) nor a change in color of the catalyst product solution could be detected.

The structures of the products **2** were unambiguously supported by $^{1}H$, $^{13}C$, DEPT-135 and COSY NMR experiments as well as IR and mass spectrometry. The molecular composition was confirmed either by HR-MS or elemental analysis (see Supporting Information). Switching to the enantioselective cycloisomerization did not show any significant changes in conversion or isolated yield, but the determination of the enantiomeric excess turned out to be very challenging with this type of enals. In fact, we did not succeed in separating the racemic mixtures [generated by application of (*rac*)-BINAP], either by chiral GC or by chiral HPLC. In order to enhance the interactions between the column material and the compound, we aimed at a more polar side chain, in detail by reducing the aldehyde functionality to the corresponding primary alcohol.

We designed a novel cycloisomerization–reduction sequence in a one-pot fashion simply by adding a consecutive borohydride reduction step. After reacting the alkynyl allyl alcohols **1** in the presence of 2.5% $[Rh(COD)Cl]_2$, 5% BINAP and 5% $AgBF_4$ in dichloroethane for 5 min, a slight excess of sodium borohydride was added to give the tetrahydrofuran-3-ylethanols **3** in good to excellent yields (Scheme 4, Table 4). Moreover, ethanol was applied to raise the solubility of the hydride species.

The structures of the products **3** were also unambiguously supported by $^{1}H$, $^{13}C$, DEPT-135 and COSY NMR experiments as well as IR and mass spectrome-

**Table 4.** Cycloisomerization–reduction sequence of alkyl- and (hetero)aryl-substituted alkyne allyl alcohols **1** to arylidenetetrahydrofuran-3-ylethanols **3**.[a]

| Entry | Alkyne allyl alcohol **1**, R = | Product | | *ee* | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | **1c**, $C_6H_5$ |  | **3a** | > 99 % | 85 |
| 2 | **1d**, 1-naphthyl |  | **3b** | –[c] | 78 |
| 3 | **1e**, *p*-anisyl |  | **3c** | > 99 % | 68 |
| 4 | **1g**, *p*-tolyl |  | **3d** | > 99 % | 95 |
| 5 | **1h**, *p*-nitrophenyl |  | **3e** | –[c] | 53 |
| 6 | **1j**, *p*-bromophenyl |  | **3f** | > 99 % | 64 |
| 7 | **1n**, 2-thienyl |  | **3g** | –[c] | 87 |
| 8 | **1o**, 3-(*N*-tosyl)indolyl |  | **3h** | > 99 % | 83 |

[a] *Reaction conditions:* 1.0 equiv. of alkynyl allyl alcohol **1** (0.2 M in dichloroethane), 0.025 equiv. of $[RhCl(cod)]_2$, 0.05 equiv. of BINAP, 0.05 equiv. of $AgBF_4$ solution (0.05 M in dichloroethane).

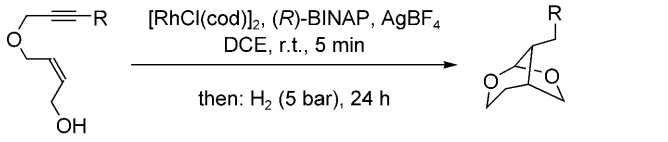
[b] Yields refer to isolated yields of compound **3**.

[c] The *ee* could not been estimated, no separation of racemic mixture on chiral GC or HPLC.

try. The molecular composition was confirmed either by HR-MS or elemental analysis (see Supporting Information). Excluding substrate **1h**, all sequential transformations led to the expected arylidenetetrahydrofuran-3-ylethanols **3**. The transformation of **1h** yielded the compound **3e** with 53% bearing an amino substituent at the aromatic system (Table 4, entry 5). Apparently, a reduction of the initial nitro group took place. Referring to literature the reduction of aromatic nitro compounds to the corresponding anilines has been accomplished with various combinations of stoichiometric amounts of sodium borohydride and metal catalysts, for example, $NiCl_2$,[13] $(py)_3RhCl_3$,[14] Cu(II) acetylacetonate,[15] Pd/C,[16] phthalocyanatoiron(II)[17] and Raney Ni.[18] To check whether the reduction is induced by an *in situ* generated rhodium hydride species we did a cross-check experiment and isolated the enal **2h**. The transformation of **2h** with 2 equivalents of sodium borohydride in dichloroethane and ethanol gave a non-separable mixture of **3e** and the corresponding nitro-substituted tetrahydrofuran-3-ylethanol. The reduction of the nitro group is therefore at least to a certain degree initiated by the sodium borohydride species without any rhodium catalyst interference. Studies addressing the scope and limitations of this unusual reduction of the aromatic nitro group are currently underway.

Concerning the *ee* determination of compounds **3**, (*rac*)-**3a**, (*rac*)-**3c**, (*rac*)-**3d**, **3f** and **3g** could successfully be separated using chiral HPLC and the *ee* of the enantiomerically pure (*R*)-configured products exceeded 99%.




**Scheme 5.** Enantioselective CIHIA sequence of alkyl- and aryl-substituted alkynyl allyl alcohols **1** to 2,7-dioxabicyclo-[3.2.1]octanes **4**.

To synthesize these novel enantioselective products in a more elegant way we considered to substitute the stoichiometric reduction step by a catalytic carbonyl hydrogenation. Referring to the cycloisomerization reactions, neither precipitation nor a change in color of the catalyst product solution could be detected. This observation encouraged us to test the possibility of performing sequential catalysis with the obviously intact rhodium catalyst system. The concept was to transform the alkynyl allyl alcohols based on the optimized rhodium-catalyzed cycloisomerization and to use the cationic rhodium system sequentially for a second catalytic hydrogenation reaction.

Practically, after reacting the alkynyl allyl alcohols **1** in the optimized cycloisomerization we set the reaction vessel under hydrogen pressure (5 bar) and stirred the mixture for 24 h at room temperature. Unexpectedly, we neither observed a reduction of the newly formed carbonyl side-chain to the corresponding alcohol functionality nor an olefin hydrogenation of the *exo* double bond. The enals **2** undergo an enantioselective sequential hydrogenation–isomerization–acetalization domino reaction. Thus we performed a cycloisomerization–hydrogenation–isomerization–acetalization (CIHIA) sequence forming 2,7-dioxabicyclo[3.2.1]octanes **4** in moderate to good yields (Scheme 5).

First of all we varied and optimized parameters such as catalyst loading, hydrogen pressure and reaction time in screening experiments (Table 5).

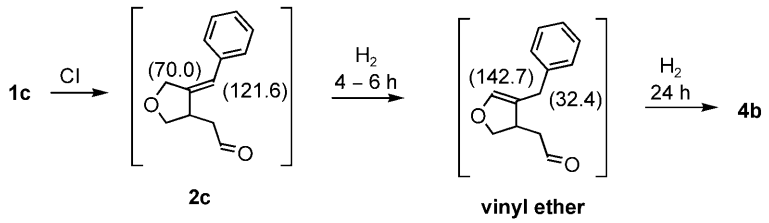
Unfortunately, a catalyst loading of 2.5% rhodium dimer, which worked very well in case of the initial cycloisomerization, did not produce a yield exceeding 50% (Table 5, entries 1–5) for the CIHIA sequence. By application of 5% rhodium precursor, a lower hydrogen pressure did not lead to a consecutive hydrogenation reaction, but isolation of the cycloisomeriza-

**Table 5.** CIHIA optimization for the reaction with **1c**.

| Entry | a) $[RhCl(cod)]^2$, b) BINAP,[a] $AgBF_4$ | Hydrogen pressure | *T*, *t* | Yield of **4b** |
|---|---|---|---|---|
| 1 | a) 2.5%, b) 5% | 1 bar | r.t., 24 h | no reaction |
| 2 | a) 2. 5%, b) 5% | 2 bar | r.t., 24 h | no reaction |
| 3 | a) 2.5%, b) 5% | 4 bar | r.t., 24 h | 30%[b]) |
| 4 | a) 2.5%, b) 5% | 5 bar | r.t., 12 h | 13%[b]) |
| 5 | a) 2.5%, b) 5% | 5 bar | r.t., 24 h | 50%[b] |
| 6 | a) 5%, b) 10% | 1 bar | r.t., 24 h | no reaction |
| 7 | a) 5%, b) 10% | 2 bar | r.t., 24 h | no reaction |
| 8 | a) 5%, b) 10% | 5 bar | r.t., 18 h | 49%[c] |
| 9 | a) 5%, b) 10% | 5 bar | r.t., 24 h | 69%[c] |

[a] (*rac*)-BINAP.
[b] Yields *via* GC.
[c] Yields refer to isolated yields of compound **4b**.




**Scheme 6.** Formation of intermediate vinyl ether (significant $^{13}C$ NMR shifts in parentheses).

tion product **2c** (Table 5, entries 6 and 7). Raising the hydrogen pressure up to 5 bar the CIHIA sequence reaches a maximum yield of 69% for compound **4c** after 24 h reaction time (Table 5, entry 9). Looking at the reaction control *via* TLC only one single product spot of the newly formed bicyclic acetal structure was detected after 24 h reaction time. Interestingly, when the CIHIA sequence was stopped after 4–6 h under hydrogen pressure, an unknown intermediate bearing a relative polarity between those of the cycloisomerization product **2c** and the corresponding acetal **4b** could be detected *via* TLC. Although the intermediate just occurs in very minor concentrations during the domino sequence, we successfully isolated a small amount of it and the $^{13}C$ as well as a DEPT-135 NMR experiment unambiguously supported the structure of the isomerized vinyl ether, a dihydrofuran derivative. (Scheme 6, spectra see Supporting Information).

Based upon these parameters (5 bar hydrogen pressure for 24 h) the CIHIA sequence for alkynyl allyl alcohols **1** was probed for some representative examples (Table 6). To the best of our knowledge these bicyclic acetal structures have not been reported in the literature and, therefore, the structures of the products **4** were unambiguously supported by $^{1}H$, $^{13}C$, DEPT-135 and COSY NMR experiments as well as IR, mass spectrometry and later by X-ray crystal structure analyses of (*rac*)-**4b** and (*R*,*R*,*R*)-**4i** (Figure 1).[19] The molecular composition was confirmed either by HR-MS or elemental analysis (see Supporting Information). For the determination of the absolute configuration by anomalous diffraction we used crystals of (*R*,*R*,*R*)-**4i** bearing the feasible heavy atom at the bromine-substituted aryl system. In complete accord with Zhang and Hashmi the cycloisomerization of **1** with (*R*)-BINAP as chelating ligand leads to (*R*)-configured enals **2**. In the CIHIA sequence this initial stereocenter induces the orientation of the stereo centers C4 and C8, whereas in the final 2,7-dioxabicyclo[3.2.1]octanes **4** all three contiguous stereocenters feature the same configuration. In short, the CIHIA sequence of **1** with (*R*)-BINAP provides the (*R*,*R*,*R*)-2,7-dioxabicyclo[3.2.1]octanes **4**.

For the subsequent description of the bicyclic acetal structures, especially within the discussion of the mechanistic rationale, we will refer to the numeration shown in Figure 1.

Most characteristically in all $^{1}H$ NMR spectra the signal of the acetal proton H1 gives a significant singlet between $\delta = 5.07$–$5.24$. The protons of the four methylene groups H3, H5, H6, and H9 and appear as discrete signal sets due to their diastereotopic character. In most cases the signals of the two stereogenic centered protons H4 and H8 cannot be clearly identified but are located as combined multiplets in the range of $\delta = 1.81$–$2.85$. The enantioselectivity of the reaction under application of the enantiomerically pure BINAP ligand and the enantiomeric excess of the resulting compounds **4b–e, 4i**, and **4k** could be obtained by chiral HPLC experiments (spectra see Supporting Information). All compounds, excluding **4k**, gave excellent *ee*s exceeding 99% (Table 6). As a matter of fact, the enantiomers of (*rac*)-**4i** could not be separated on chiral GC and the absence of UV active molecule fragments excludes separation *via* chiral HPLC. The racemic mixtures of the remaining aryl-substituted compounds **4g, 4h, 4j** and **4l** could not be separated with the chiral HPLC column on hand.

The unexpected formation of the bicyclic acetals **4** prompted us to investigate the CIHIA sequence mechanistically and to propose a mechanistic rationale of this domino sequence.

Looking at the differences in mass of the intermediate enals and the acetal product, an addition of molecular hydrogen takes place. Therefore, it is reasonable to assume a hydrogenation key step, presumably of the aldehyde functionality, generating an alcohol intermediate within the domino sequence. Hence, we carried out H/D-exchange experiments (Scheme 7) to gain an insight in the reduction key step by analyzing the position of the deuterium atoms in the final products. Besides the synthesis of **4b** (Scheme 7, A), we also conducted using **1c** in a CIHIA sequence but applying deuterium instead of hydrogen (Scheme 7, B). The isolated mixture contained the bis-deuterated compound **5a** and the mono-deuterated compound **5b** in a 1:1 ratio (determined by mass spectrometry).

The $^{1}H$ NMR data showed a simplified couple of signals for the α-methylene group C6. In comparison to the characteristic signal of the acetal-bridged hydrogen H1 the set of integrals H6 have decreased to a relative value of approximately 0.5 (Figure 1). The deuterium substituent is therefore located at both the axial and equatorial positions with a 50% distribution

**Table 6.** Rhodium(I)/BINAP-catalyzed CIHIA sequence.[a]

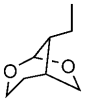
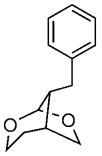
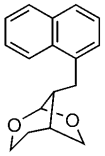
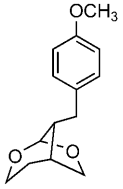
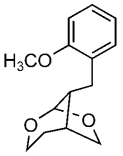
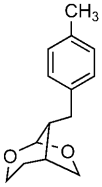
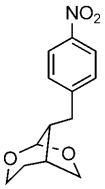
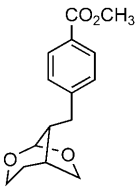
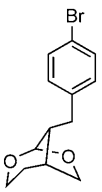
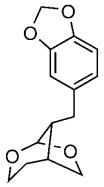
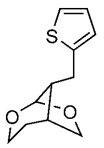
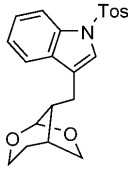
| Entry | Alkynyl allyl alcohol, R = | Product | | *ee* | Yield [%][b] |
|---|---|---|---|---|---|
| 1 | **1a**, $CH_3$ |  | **4a** | –[c] | 34[d] |
| 2 | **1c**, $C_6H_5$ |  | **4b** | >99% | 69 |
| 3 | **1d**, 1-naphthyl |  | **4c** | >99% | 35 |
| 4 | **1e**, *p*-anisyl |  | **4d** | >99% | 38 |
| 5 | **1f**, *o*-anisyl |  | **4e** | >99% | 38 |
| 6 | **1g**, *p*-tolyl |  | **4f** | >99% | 55 |
| 7 | **1h**, *p*-nitrophenyl |  | **4g** | –[c] | 70 |
| 8 | **1i**, methyl *p*-benzoate |  | **4h** | –[c] | 60 |
| 9 | **1j**, *p*-bromophenyl |  | **4i** | >99% | 54 |

**Table 6.** (Continued)

| Entry | Alkynyl allyl alcohol, R = | Product | | *ee* | Yield [%][b] |
|---|---|---|---|---|---|
| 10 | **1m**, 1,3-benzodioxol-5-yl |  | **4j** | –[c] | 58 |
| 11 | **1n**, 2-thienyl |  | **4k** | 63% | 52 |
| 12 | **1o**, 3-(*N*-tosyl)indolyl |  | **4l** | –[c] | 68 |

[a] *Reaction conditions:* 1) cycloisomerization: 1.0 equiv. of **1** (0.2 M in DCE), 0.05 equiv. of $[RhCl(cod)]_2$, 0.1 equiv. of BINAP, 0.1 equiv. of $AgBF_4$ solution (0.05 M in DCE). 2) $H_2$ pressure (5 bar).
[b] Yields refer to isolated yields of compound **4**.
[c] The *ee* could not been estimated, no separation of racemic mixture on chiral GC or HPLC.
[d] Highly volatile compound.

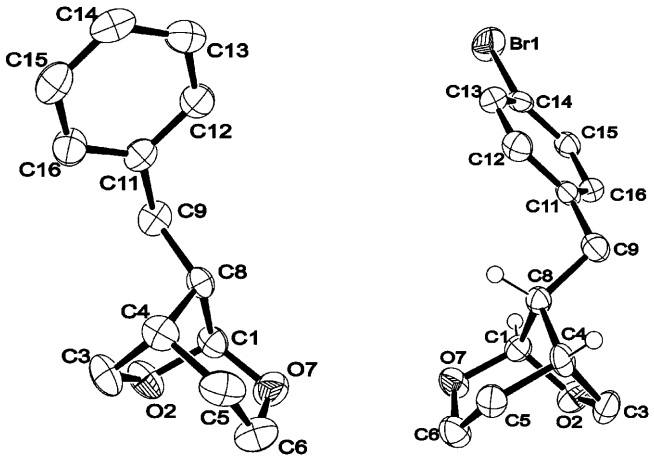


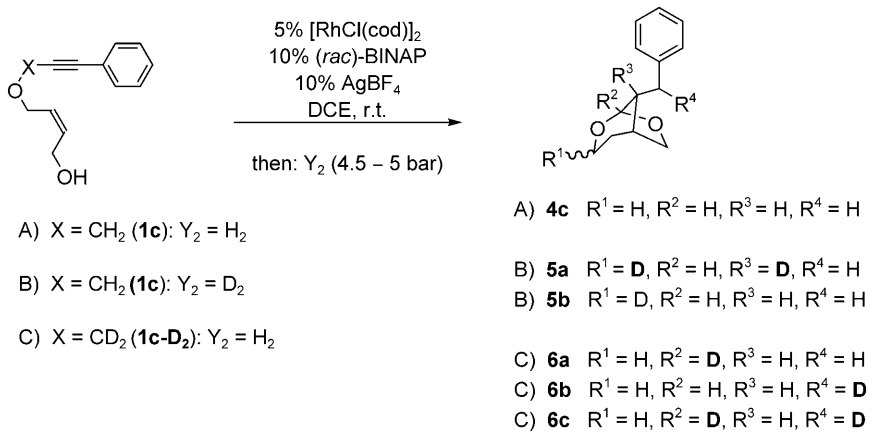

**Figure 1.** Molecular structure of (*S*,*S*,*S*)-**4b** (*left*) and (*R*,*R*,*R*)-**4i** (*right*). Most hydrogen atoms have been omitted for clarity.

each. For compound **5b** the second deuterium substituent can be found at the stereocenter C8 with a relative integral of 0.4 amounting to approximately 50% deuteration. As the deuterated carbon atom correlates with the former carbon center of the aldehyde functionality, this indicates an intermediate deuteration of the carbonyl group to the corresponding deuterated alcohol side-chain.

The counter experiment, the hydrogenation sequence with the corresponding deuterated alkyne allyl alcohol **1c-$D_2$**, was also conducted generating a mixture of two mono-deuterated compounds **6a** and **6b** and the bis-deuterated compound **6c** (Scheme 7, C). The ratio of the mono-deuterated compound *vs.* the bis-deuteration products showed a 1:8 excess of **6c** (determined by mass spectrometry). In contrast, the deuterium substituents are found at the acetal bridge atom C1 and in the α-position to the phenyl moiety (C9). Interestingly, looking at the sets of signals of H9 in the α-position to the phenyl moiety, only the integral of one of the two signals decreases to a relative value of 0.3 whereas the other integral area remained at 1.0. This means the methylene group next to the phenyl moiety has selectively been deuterated at one of the diastereotopic positions. After the cycloisomerization reaction the $CD_2$ group next to the *exo*-cyclic double bond forms the only deuterium source, therefore, an isomerization reaction from allyl ether to the corresponding vinyl ether seems to be reasonable. As no deuterium was found at the stereo center C8 the stereosepecific deuterium transfer excludes a possible hydrorhodation step. The minor hydrogen content at carbon atom C9 indicates a hydrogen/deuterium scrambling.

Assuming a combination of a rhodium-catalyzed hydrogenation as well as an allyl ether-vinyl ether isomerization, we synthesized specially modified model compounds, derived from compound **1c** to selectively block out one of the above-mentioned reaction steps. Firstly we converted the ester tethered analogue **7** in

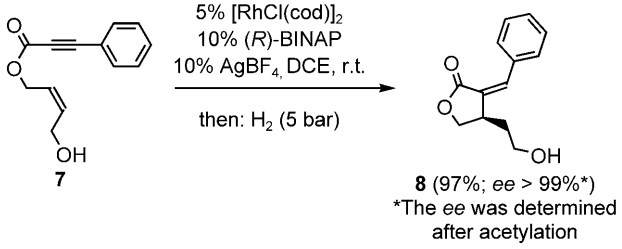
  




**Scheme 7.** CIHIA experiments with H/D exchange.

the cycloisomerization under the established conditions into the corresponding lactone. Application of the hydrogenation sequence resulted in the reduction of the carbonyl functionality to give the alcohol **8**[20] (Scheme 8). As expected the Michael system within the lactone core prevents any migration of the exocyclic double bond and any subsequent ring closure but leads to the corresponding lactone with a primary alcohol side chain.

In another approach we methylated the cycloisomerization-reduction product **3a** and subjected the resulting methyl ether **9** to the standard hydrogenation conditions (Scheme 9). The GC-MS analysis of the product mixture (70% yield based on recovered starting material) revealed the peaks of three newly

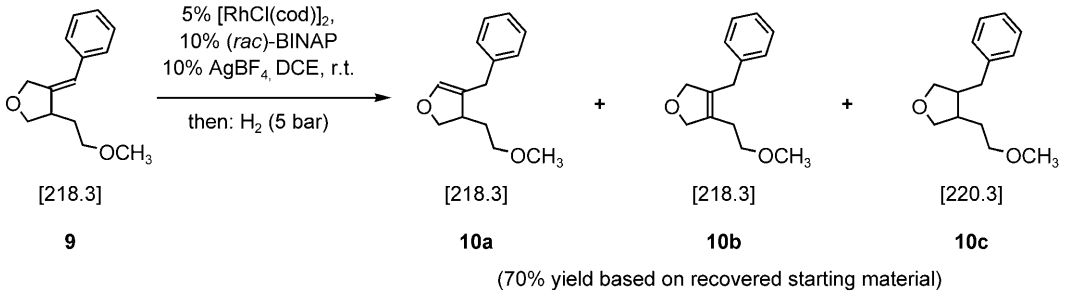



**Scheme 8.** Cycloisomerization–hydrogenation sequence of **7** to **8**.

formed compounds, whereas twice $m/z = 218$ ($R_f =$ 23.7 min and 25.9 min, **10a** and **10b**) and once $m/z =$ 220 ($R_f = 24.6$ min, **10c**) were detected (ratio [218]:[218]:[220] = 1:2.3:8.8). For comparison, the starting material **9** was also analyzed by GC-MS under the same conditions ($R_f = 26.8$ min). Unfortunately, the products **10a–c** could not be separated by column chromatography.

The main product **10c** was derived from a rhodium-catalyzed hydrogenation. Although the NMR data of the mixture were not very significant they clearly proved the migration of the benzylic double bond. By comparison of the $^1$H NMR spectra of starting material **9** with product mixture **10a–c**, the singlet signal of the former *exo*-olefinic hydrogen atom ($\delta = 6.34$) has disappeared. Similarly, the signal of the methylene group between the oxygen atom and the *exo*-cyclic double bond, formerly appearing as singlet signal at $\delta = 4.61$, dropped out. However, the $^1$H NMR spectrum of **10a–c** bears a multiplet ($\delta = 5.01$–$5.10$) and hereby gives a considerable indication for the hydrogen atom of a vinyl ether. We ascribe the formation of the vinyl ether **10a** and the achiral dihydrofuran **10b** to a rhodium-catalyzed isomerization reaction.

As we have observed no subsequent domino reaction after the cycloisomerization without any parameter changes, we believe that the active rhodium hy-

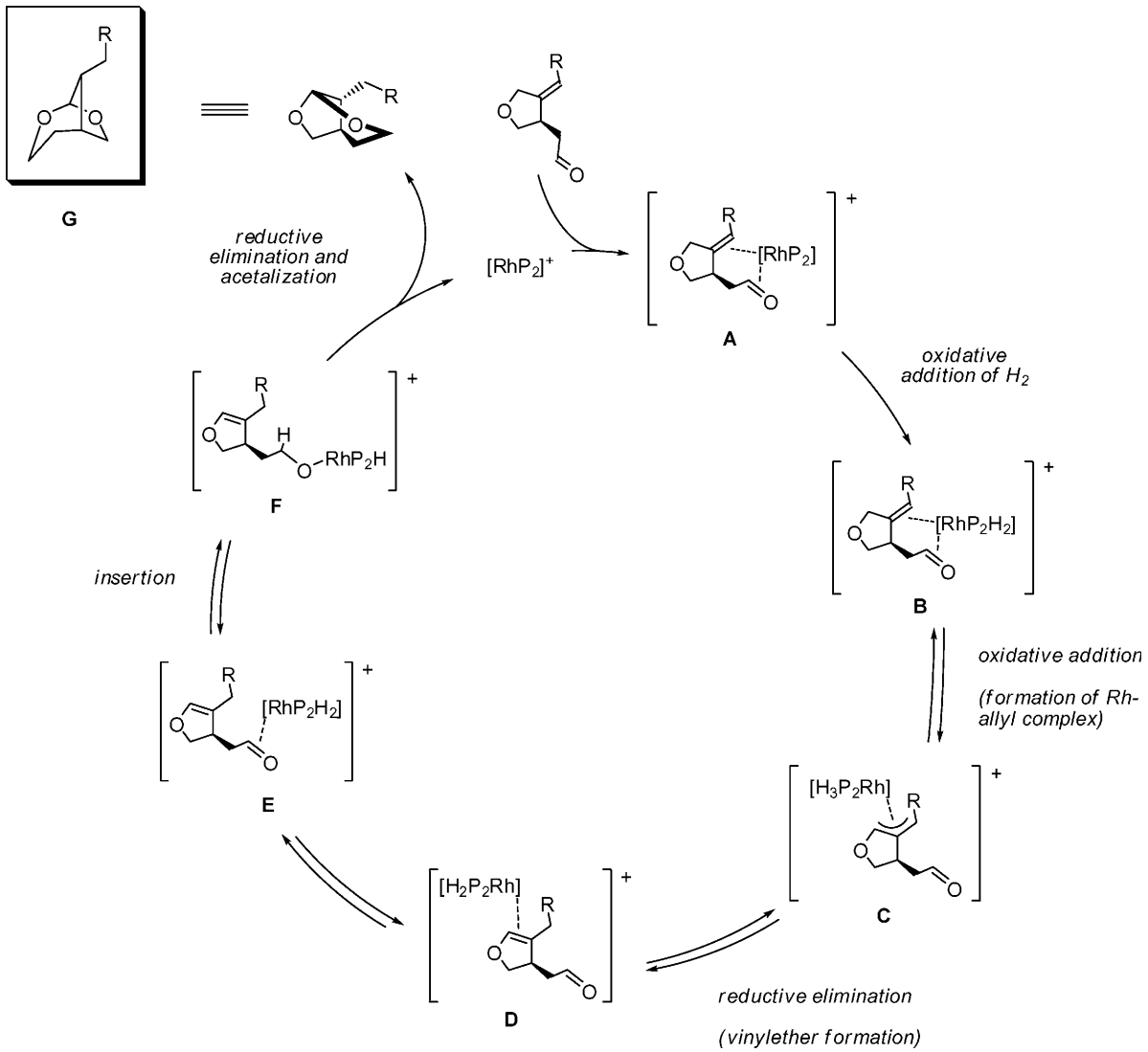



**Scheme 9.** Hydrogenation experiment with **9**.

dride catalyst species for the subsequent domino sequence is generated by the application of increased hydrogen pressure. To further prove our postulate of an active rhodium(III) hydride species within the scope of the isomerization key step, we subjected alcohol **3a** first to the cationic rhodium-BINAP species under an argon atmosphere and secondly under a hydrogen atmosphere. In the first case we only observed a very minor formation of the corresponding acetal **4b** *via* GC. Application of the hydrogen atmosphere, hence generation of a rhodium(III)-hydride species, led to quantitative formation of **4b**. We conclude a very slow isomerization rate of the rhodium(I), but in the case of the rhodium(III) hydride species a significant acceleration can be observed. The general isomerization potential of rhodium hydride complexes *via* an allyl rhodium species has already been reported.[21] In our case, the isomerization of the allyl ether to the vinyl ether by means of an active rhodium(III) hydride species implies the generation of a rhodium(V) hydride allyl intermediate. Examples of rhodium(V) intermediates and complexes, although they still remain limited, can be found within studies by Maitlis et al. and Beckett et al.[22]

Based on the presented H/D exchange experiments and additional hydrogenation and isomerization investigations, respectively, we propose the following mechanistic rationale (Scheme 10). After the cycloisomerization reaction and generation of the (*R*)-configured enal, the cationic rhodium/(*R*)-BINAP complex **A**, coordinated to the carbonyl and the allyl ether double bonds, undergoes an oxidative addition with molecular hydrogen to give the active cationic rhodium hydride catalyst **B**. The newly formed rhodium(III) hydride species catalyzes an isomerization of the allyl ether compound **B** to the corresponding vinyl ether analogue **D**, which we were able to isolate, *via* formation of a rhodium(V) allyl intermediate. The al-




**Scheme 10.** Proposed mechanism for the rhodium/(*R*)-BINAP-catalyzed CIHIA sequence.

ternative hydrorhodation mechanism can be excluded by the results of the hydrogenation experiment leading to the acetals **6a–c**. The isomerization *via* the allyl complex is accompanied by a primary isotope effect as well as a favored stereospecific-*syn* hydrogen transfer. This concept delivers a reasonable explanation for the exclusive H-transfer in case of the deuterium experiment (product **5a**, **b**) and the H/D scrambling for the hydrogenation of the deuterated starting material (**6a–c**). Coordination to the carbonyl double bond (**E)** sets the stage for the aldehyde reduction by insertion of the rhodium(III) hydride (**F**). By final reductive elimination and acetalization the (*R*,*R*,*R*)-configured bicyclic acetal **G** and the original cationic rhodium/(*R*)-BINAP species are released. As we could not prove whether the cyclizing acetalization takes place under rhodium catalysis, a formal Lewis or Brønsted acid-catalyzed cyclization cannot be excluded. The facial attack of the hydroxy functionality within the acetalization step derives from the configuration of the stereocenter generated in the preceding cycloisomerization reaction whereas in the acetal product **4b** the phenyl substituent points into the direction of the five-membered ring system, the former tetrahydrofuran system.

## Conclusions

Starting from a rhodium/BINAP-catalyzed cycloisomerization of alkynyl allyl alcohols **1** to novel substituted alkylidene and arylidene tetrahydrofurans **2**, we have developed a cycloisomerization–reduction sequence giving arylidene tetrahydrofuran-3-ylethanols **3** in good yields and with excellent *ee* $> 99\,\%$. In particular, we elaborated an enantioselective one-pot CIHIA sequence to 2,7-dioxabicyclo[3.2.1]octanes **4** and investigated the mechanism of this novel reaction sequence.

## Experimental Section

The catalysis reactions were performed in degassed dichloroethane which was dried using an MBraun system MB-SPS-800. All rhodium-catalyzed cycloisomerization reactions were carried out in oven-dried Schlenk glassware using septa and syringes under an argon atmosphere. All rhodium-catalyzed one-pot sequences based on the cycloisomerization reaction were performed in purpose-made Schlenk tubes (6 mL volume, 4 mm wall thickness to resist the excess hydrogen pressure). The purification of products was performed on silica gel 60 (0.015–0.040 mm) using the flash technique and under pressure of 2 bar. The crude mixtures were adsorbed on Celite 545 (0.02–0.10 mm) before chromatographic purification. The reaction progress was monitored qualitatively using TLC silica gel 60 F254 aluminium sheets. The spots were detected using ethanolic solution and the $R_f$ values are listed with the corresponding solvent mixtures. The $^1$H and $^{13}$C NMR spectra were recorded on a Bruker DRX 500 and an Avance DRX 250 spectrometer. TMS was used as reference ($\delta = 0.0$) or the resonance of $CDCl_3$ was locked as internal standard ($^1$H: $\delta = 7.24$, $^{13}$C: $\delta = 77.0$). The multiplicities of signals are abbreviated as s (singlet), d (doublet), t (triplet), dd (doublet of doublets), m (multiplet) and corresponding combinations. The type of carbon atoms ($CH_3$, $CH_2$, CH, $C_{quat}$) was determined on the basis of DEPT-135 NMR spectra. EI-mass spectra were measured on a Finnigan MAT 8200 spectrometer. IR spectra were obtained on a Bruker Vector 22 FT-IR. The solids were measured as KBr pellets and the oils in the form of films on KBr plates. The intensity of signals is abbreviated as s (strong), m (medium) and w (weak). The melting points (uncorrected) were measured on a Büchi Melting Point B-540. Combustion analyses were carried out on a Perkin–Elmer Series II Analyser 2400 in the microanalytical laboratory of the Institut für Pharmazeutische und Medizinische Chemie der Heinrich Heine Universität Düsseldorf.

### Typical Procedure for the Sonogashira Coupling Reaction of the Aryl-Substituted Alkynyl Allyl Alcohols 1

**(*Z*)-4-[3-(3,4,5-Trimethoxyphenyl)prop-2-ynyloxy]but-2-en-1-ol (1l):** In a 100-mL Schlenk flask 2.0 g (6.8 mmol) 5-iodo-1,2,3-trimethoxybenzene and 0.88 g (1.03 equiv., 7.0 mmol) (*Z*)-4-(prop-2-ynyloxy)but-2-en-1-ol were dissolved in 20 mL absolute THF under an argon atmosphere at room temperature. To the yellowish solution 49 mg (1%, 0.07 mmol) dichlorobis(triphenylphosphane)palladium(II) and 14 mg (1%, 0.07 mmol) copper(I) iodide were added resulting in a yellow suspension The reaction was finally started by addition of 30 mL of distilled triethylamine whereby the suspension turned into a brown solution immediately. The reaction mixture was stirred at room temperature overnight (18 h) and the conversion checked *via* TLC and/or GC-MS.

The precipitate was filtered off and the filtrate poured into water. After several extraction steps with diethyl ether the combined organic phases were washed with water and brine. Finally the organic phase was dried with anhydrous magnesium sulfate and the solvents were removed under vacuum and the residual crude product was chromatographed on silica gel (*n*-hexane/diethyl ether 1:2, $R_f = 0.35$) to give the analytically pure product **1l** in the form of a yellow solid; yield: 1.73 g (5.9 mmol, 84%); mp 54 °C. $^1$H NMR ($CDCl_3$, 300 MHz): $\delta = 1.73$ (s, 1H), 3.82 (s, 9H), 4.20 (d, $J = 6.5$ Hz, 2H), 4.24 (d, $J = 6.5$ Hz, 2H), 4.35 (s, 2H), 5.69–5.73 (m, 1H), 5.82–5.87 (m, 1H), 6.67 (s, 2H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta = 56.3$ ($CH_3$), 58.3 ($CH_2$), 58.9 ($CH_2$), 61.2 ($CH_3$), 65.3 ($CH_2$), 84.0 ($C_{quat}$), 86.8 ($C_{quat}$), 109.2 (CH), 117.6 ($C_{quat}$), 127.9 (CH), 133.2 (CH), 139.2 ($C_{quat}$), 153.2 ($C_{quat}$); EI-MS (70 eV): *m/z* (%) = 292 ($[M]^+$, 22), 261 ($[M-CH_3O]^+$, 12), 231 ($[M-C_2H_5O]^+$, 34), 222 ($[M-C_4H_6O]^+$, 15), 215 (20), 206 (30), 205 ($[M-C_4H_7O_2]^+$, 100), 195 (35), 193 (11), 192 (18), 191 ($[M-C_5H_9O_2]^+$, 84), 189 ($[C_{11}H_9O_3]^+$, 18), 181 ($[C_{10}H_{13}O_3]^+$, 27), 176 (18), 175 ($[C_{11}H_{11}O_2]^+$, 15), 173 ($[C_{11}H_9O_2]^+$, 12), 172 (42), 169 (19), 168 ($[C_9H_{12}O_3]^+$, 16), 163 (37), 162 (22), 161 (20), 160 ($[C_{10}H_8O_2]^+$, 18), 145 (13), 131 (20), 119 (19), 115

($[C_6H_{11}O_2]^+$, 12), 105 (18), 103 (25), 102 ($[C_5H_{10}O_2]^+$, 18), 91 (31), 89 ($[C_4H_9O_2]^+$, 19), 77 (21), 71 ($[C_4H_7O]^+$, 6). IR (KBr): $\tilde{\nu}=3364$ (br), 2943 (m), 2838 (m), 2365 (w), 2345 (w), 2228 (w), 1577 (s), 1543 (w), 1508 (s), 1459 (m), 1438 (w), 1411 (m), 1341 (m), 1238 (s), 1184 (w), 1130(s), 1082 (m), 1026 (m), 993 (m), 933 (w), 834 (m), 772 (w), 676 (w), 631 (m), 527 $cm^{-1}$ (w); anal. calcd. for $C_{16}H_{20}O_5$ (292.13): [%] C 65.74, H 6.90; found: C 65.70, H 6.73.

## Typical Procedure for the Rhodium-BINAP-Catalyzed Cycloisomerization of Alkyl- and Aryl-Substituted Alkynyl Allyl Alcohols 1 to γ,δ-Enals 2

**(*Z*)-2-[4-(Thiophen-2-ylmethylene)tetrahydrofuran-3-yl]-acetaldehyde (2n):** Under an argon atmosphere 12.3 mg (0.025 mmol) of the $[RhCl(cod)]_2$ precursor and 31.1 mg (0.05 mmol) (*R*)-BINAP ligand were placed in a Schlenk tube. Then 4 mL dried, degassed dichloroethane was added and the solution was stirred for several minutes, until a dark red solution was formed. Then 208 mg (1.0 mmol) alkyne allyl alcohol **1n** were added, the solution stirred for another minute and finally the reaction was started by addition of 1 mL (0.05 mmol) of $AgBF_4$ solution (*c* 0.05 M, dissolved in dichloroethane). The reaction was monitored by TLC and full conversion was observed after 5 min at room temperature. After dilution with diethyl ether the crude product was filtered, the solvents removed under vacuum, and the residue was chromatographed on silica gel (*n*-hexane/diethyl ether 1:2, $R_f=0.43$) to give the analytically pure product **2n** in form of a yellow oil; yield: 197 mg (0.95 mmol, 95%). $^1$H NMR ($CDCl_3$, 300 MHz): $\delta=2.70$ (ddd, $J=18.2$ Hz, $J=8.4$ Hz, $J=1.1$ Hz, 1H), 2.84 (ddd, $J=18.2$ Hz, $J=5.1$ Hz, $J=1.2$ Hz, 1H), 3.30–3.39 (m, 1H), 3.59 (dd, $J=8.8$ Hz, $J=5.5$ Hz, 1H), 3.81 (s, 3H), 4.13 (dd, $J=8.8$ Hz, $J=6.5$ Hz, 1H), 4.59–4.61 (m, 2H), 6.55–6.58 (m, 1H), 6.88 (d, $J=3.6$ Hz, 1H), 7.03 (dd, $J=5.1$ Hz, $J=3.6$ Hz, 1H), 7.26–7.29 (m, 1H), 9.84 (t, $J=1.1$ Hz, 1H); $^{13}$C NMR ($CDCl_3$, 75.5 MHz): $\delta=39.2$ (CH), 47.4 ($CH_2$), 70.4 ($CH_2$), 73.1 ($CH_2$), 114.3 (CH), 125.6 (CH), 126.2 (CH), 127.5 (CH), 140.6 ($C_{quat}$), 142.0 ($C_{quat}$), 200.5 (CH); EI MS (70 eV):, *m/z* (%) = 208 ($[M]^+$, 59), 179 ($[M-(CHO)]^+$, 6), 165 ($[C_9H_9O_2]^+$, 15), 164 ($[M-(CO_2)]^+$, 84), 151 ($[C_8H_7OS]^+$, 18), 149 ($[C_8H_6OS]^+$, 21), 138 ($[C_7H_6OS]^+$, 22), 135 ($[C_8H_7S]^+$, 67), 123 ($[C_7H_7S]^+$, 15), 113 ($[C_6H_9O_2]^+$, 100), 110 ($[C_6H_6S]^+$, 36), 109 ($[C_6H_5S]^+$, 16), 97 ($[C_5H_5S]^+$, 96), 91 ($[C_7H_7]^+$, 18), 85 ($[C_4H_5S]^+$, 20), 84 ($[C_4H_4S]^+$,17), 69 ($[C_4H_5O]^+$, 27); IR (film): $\tilde{\nu}=3411$ (s), 3104 (m), 2939 (s), 2846 (s), 2727 (m), 2364 (w), 2248 (w), 1722 (s), 1675 (m), 1514 (w), 1474 (w), 1429 (m), 1403 (m), 1385 (m), 1310 (m), 1231 (m), 1065 (s), 933 (s), 854 (m), 702 (s), 666 (w), 509 $cm^{-1}$ (m); UV/Vis ($CH_2Cl_2$): $\lambda_{max}$ (ε) = 272 nm (11200), 282 nm (14700), 292 (11000); HR-MS: *m/z* = 208.0564, calcd. for $[C_{11}H_{12}O_2S]$: 208.0558; (*R*)-enantiomer: $[\alpha]_D^{20}$: −14.4° (*c* 1.0 M, $CHCl_3$).

## Typical Procedure for the Enantioselective Cycloisomerization-Reduction Sequence to Tetrahydrofuran-3-yl)ethanols

**(*R*,*Z*)-2-[4-(4-Methylbenzylidene)tetrahydrofuran-3-yl]ethanol (3d):** Under an argon atmosphere 6.2 mg (0.0125 mmol) of the $[RhCl(cod)]_2$ precursor and 15.6 mg (0.025 mmol) (*R*)-BINAP ligand were placed in a Schlenk tube. Then 2 mL degassed dichloroethane were added and the solution was stirred for several minutes, until a dark red solution was formed. Then 108 mg (0.5 mmol) **1g** was added, the solution stirred for another minute and finally the reaction was started by addition of 0.5 mL $AgBF_4$ (dissolved in dichloroethane, *c* 0.5 M). The reaction was monitored by TLC and showed a complete conversion after 5 min at room temperature. Then 38 mg (1.0 mmol) sodium borohydride and 0.5 mL ethanol were added and the mixture stirred at room temperature for 30 min. The reaction was again checked by TLC. The excess of sodium borohydride was destroyed by dropwise addition of 2 N hydrochloric acid. After addition of water and extraction with diethyl ether the combined organic layers were dried with anhydrous sodium sulfate, filtered, the solvents removed under vacuum and the residue was chromatographed on silica gel (diethyl ether, $R_f=0.20$) to give the analytically pure product **3d** in the form of a yellow oil; yield: 104 mg (0.48 mmol, 95%). $^1$H NMR ($CDCl_3$, 500 MHz): $\delta=1.70$–$1.76$ (m, 2H), 1.94–2.00 (ddd, $J=13.5$ Hz, $J=12.0$ Hz, $J=6.7$ Hz, 1H), 2.32 (s, 3H), 2.94–2.99 (m, 1H), 3.64 (dd, $J=8.5$ Hz, $J=5.3$ Hz, 1H), 3.73 (t, $J=6.4$ Hz, 2H), 3.99 (dd, $J=8.5$ Hz, $J=6.5$ Hz, 1H), 4.57–4.65 (m, 2H), 6.33 (d, $J=2.1$ Hz, 1H), 7.01 (d, $J=8.1$ Hz, 2H), 7.13 (d, $J=7.9$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta=21.3$ ($CH_3$), 36.3 ($CH_2$), 42.9 (CH), 61.2 ($CH_2$), 70.3 ($CH_2$), 72.9 ($CH_2$), 121.1 (CH), 128.1 (CH), 129.4 (CH), 134.6 ($C_{quat}$), 136.7 ($C_{quat}$), 143.7 ($C_{quat}$). IR (film): $\tilde{\nu}=3385$ (s), 2939 (s), 2865 (s), 1653 (w), 1610 (w), 1514 (s), 1456 (m), 1361 (m), 1183 (m), 1054 (s), 927 (m), 882 (w), 810 (m), 435 (s), 427 $cm^{-1}$ (s); EI-MS (70 eV): *m/z* = 218 ($[M]^+$, 4), 201 ($[M-OH]^+$, 2), 145 ($[C_{10}H_{11}O]^+$, 14), 136 (33), 132 (11), 131 (11), 129 ($[C_{10}H_9]^+$,12), 121 (65), 120 (83), 119 ($[C_9H_{11}]^+$, 100), 118 (13), 117 (10), 115 (15), 114 (20), 113 (13), 106 (65), 105 (85), 99 (20), 93 (16), 92 (16), 91 ($[C_7H_7]^+$, 96), 83 (18), 77 (15), 71 ($[C_4H_7O]^+$,15); HR-MS: *m/z* = 218.1285, calcd. for $C_{14}H_{18}O_2$: 218.1307; (*R*)-enantiomer: $[\alpha]_D^{20}$: −0.5° (*c* 1.0 M, $CHCl_3$); chiral HPLC (*n*-hexane/2-PrOH 95:5, 0.6 mL $min^{-1}$, 254 nm): $t_R=40.0$ min (major), $t_S=46.0$ min (minor): *ee* > 99%.

## Typical Procedure for the Enantioselective Cycloisomerization–isomerization–hydrogenation–acetalization Sequence to 2,7-Dioxabicyclo[3.2.1]octanes

**8-(4-Nitrobenzyl)-2,7-dioxabicyclo[3.2.1]octane (4g):** Under an argon atmosphere 12.3 mg (0.025 mmol) of the $[RhCl(cod)]_2$ precursor and 31.1 mg (0.05 mmol) (*R*)-BINAP ligand were placed in a Schlenk tube (8 mL volume, 4 mm wall thickness). Then 4 mL degassed dichloroethane were added and the solution was stirred for several minutes, until a dark red solution was formed. Then 124 mg (0.5 mmol) alkyne allyl alcohol **1h** were added, the solution stirred for another minute and finally the reaction was started by addition of 1 mL (0.05 mmol) of $AgBF_4$-solution (*c* 0.05 M, dissolved in dichloroethane). The solution was stirred for 10 min at room temperature before the reaction vessel was set under hydrogen pressure (5 bar) for 24 h. After dilution with diethyl ether the crude product was filtered, the solvents removed under vacuum and the residue was chromatographed on silica gel (*n*-hexane/diethyl ether 1:2) to give the analytically pure product **4g** in the form of a

colorless solid; yield: 87 mg (0.35 mmol, 70%); mp 103 °C. $^1$H NMR ($CDCl_3$, 500 MHz): $\delta = 1.55$ (dt, $J = 13.1$ Hz, $J = 4.3$ Hz, 1H), 1.80 (dd, $J = 19.6$ Hz, $J = 12.8$ Hz, 1H), 2.20 (t, $J = 8.0$ Hz, 1H), 2.30 (s, 1H), 2.50 (dd, $J = 14.0$ Hz, $^3J = 8.1$ Hz, 1H), 2.68 (dd, $J = 14.0$ Hz, $J = 7.8$ Hz, 1H), 3.71 (dd, $J = 11.7$ Hz, $J = 6.8$ Hz, 1H), 3.82 (td, $J = 12.2$ Hz, $J = 12.1$ Hz, $J = 4.5$ Hz, 1H), 4.03 (d, $J = 8.5$ Hz, 1H), 4.08 (m, 1H), 5.09 (s, 1H), 7.31 (d, $J = 8.6$ Hz, 2H), 8.14 (d, $J = 8.7$ Hz, 2H); $^{13}$C NMR ($CDCl_3$, 125 MHz): $\delta = 31.3$ ($CH_2$), 34.8 ($CH_2$), 36.2 (CH), 51.4 (CH), 59.0 ($CH_2$), 70.7 ($CH_2$), 102.0 (CH), 123.8 (CH), 129.6 (CH), 146.7 ($C_{quat}$), 147.1 ($C_{quat}$). EI MS (70 eV): *m/z* (%) = 249 ([M]$^+$, 7), 203 ([M−$NO_2$)]$^+$, 6), 186 (19), 158 (8), 156 (10), 149 ([$C_8H_7NO_2$]$^+$, 15), 142 (16), 137 ([$C_7H_5NO_2$]$^+$, 15), 129 (43), 128 (51), 127 ([$C_7H_{11}O_2$]$^+$, 14), 119 (30), 116 (23), 115 ([$C_6H_{11}O_2$]$^+$, 46), 107 (21), 103 (24), 102 (13), 91 (42), 90 (40), 83 (41), 79 (10), 78 (49), 77 ([$C_6H_5$]$^+$, 42), 67 (100); IR (KBr): $\tilde{\nu} = 3109$ (m), 3081 (s), 2990 (m), 2957 (s), 2882 (s), 2451 (s), 2217 (w), 1942 (m), 1810 (m), 1721 (m), 1602 (s), 1508 (s), 1447 (m), 1385 (w), 1342 (s), 1283 (w), 1243 (s), 1229 (m), 1205 (m), 1188 (m), 1160 (m), 1094 (s), 1042 (s), 997 (s), 9245 (s), 857 (s), 832 (m), 818 (m), 781 (w), 746 (m), 698 (s), 650 (m), 618 (m), 536 (s), 525 cm$^{-1}$ (m); anal. calcd. for $C_{13}H_{15}NO_4$ (249.10): [%] C 62.64, H 6.07, N 5.62; found: C 62.64, H 6.42, N 5.57; $[\alpha]_D^{20}$: −74.7° (*c* 1.0 M, $CHCl_3$).

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[19] CCDC 739867 [(*rac*)-**4b**] and CCDC 739868 [(*R,R,R*)-**4i**)] contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif [or from the Cambridge Crystallographic Data Center, 12 Union Road, Cambridge CB2 1EZ, UK; fax: (+44)- 1223–336–033; or deposit@ccdc.cam.ac.uk].

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