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Diastero- and enantioselective intramolecular carbometalation reaction

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This paper is dedicated to Professor Brian Stoltz in honor of his Tetrahedron Award

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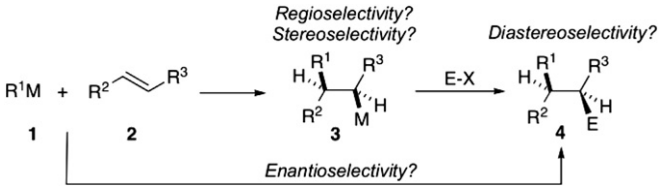
ABSTRACT

The zinc-catalyzed addition of various alkynes to acylsilanes followed by a Zn-Brook rearrangement and either the Zn-ene-allene or Zn-yne-allene cyclization led to the enantio- and diastereoselective formation of carbocycles in a single-pot operation.

1. Introduction

Addition of a carbon–metal bond of an organometallic **1** across a carbon–carbon double bond **2**, leading to a new organometallic **3** in which the newly formed carbon–metal bond of **3** can be used for further synthetic transformations to give **4** are called carbometalation reactions[1] (Scheme 1). To be synthetically useful, the new organometallic **3** must have a reactivity different from that of **1** to avoid oligomerization of the carbometalated substrate. So, the carbometalation ability of **1** must be higher than that of **3**, except in the case of an intramolecular carbometalation reaction, where entropy factors favor the mono-addition even if the starting organometallic and the product has similar reactivities. If an efficient method would be available to render such a method asymmetric, it would acquire significant utility as a method for the creation of asymmetric stereocenters. Although the enantioselective carbometalation reaction of double carbon–carbon bonds has a huge potential in synthesis, it has not yet reached its promise due to the difficulty of enantiofacial differentiation of unactivated alkenes.[2] Even more challenging would be to render such approach enantioselective through asymmetric catalysis.[3]



Scheme 1.

In the last few years, it has become abundantly clear that zinc-ene cyclizations have a great potential in organic synthesis,[4] and in this context, we have initially developed the zinc-ene-allene carbocyclization through a metalation of propargylic hydrogens followed by a transmetalation into an allenylzinc species and subsequent cyclization.[5] This strategy was extended to the stereoselective syntheses of polysubstituted tetrahydrofurans,[6] pyrrolidines,[7] and to an efficient approach to angular and linear triquinane skeletons,[8] as well as to the zinc-yne-allene[9] carbocyclization reactions. This initial approach was further improved when it was found that a tandem Zn-promoted Brook rearrangement/carbocyclization reaction also leads to cyclic product in similar yields (70–80%) with complete diastereoselectivity (Scheme 2).[10]

Various alkynylmagnesium bromide derivatives **5** were added to acylsilane **6** over a period of 30 min to lead to the corresponding

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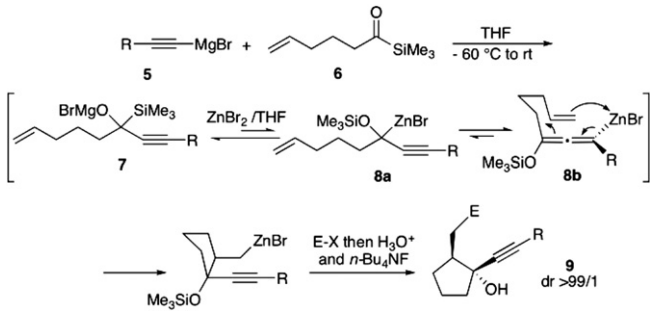
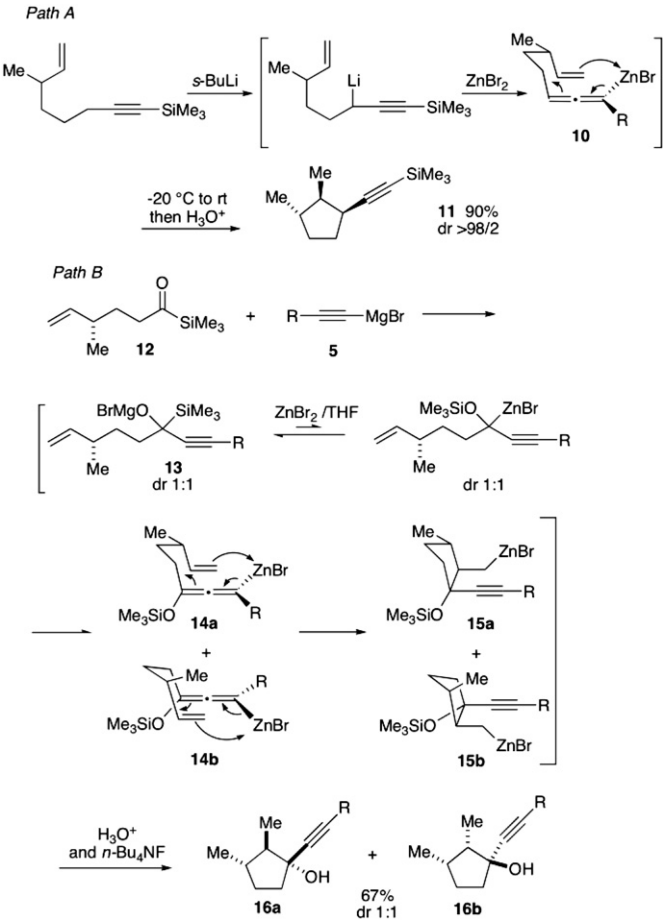


Scheme 2.

α-metallooxypropargylsilanes **7**. Then, by addition of one equivalent of zinc bromide, a Zn-Brook rearrangement proceeds to give the corresponding propargyl **8a**/allenylzinc **8b** derivatives, that is, immediately followed by a diastereoselective Zn-ene-allene cyclization reaction leading to the cyclic product **9** as a unique diastereoisomer (Scheme 2).[10] The reaction proceeds smoothly for all tested metalated alkynes (R=$SiMe_3$, R=Ph, and R=Hex) and the formation of an organometallic species was checked by reaction with electrophiles. The unique *cis*-configuration could be rationalized by a zinc-ene-allene transition state **8b** as illustrated in Scheme 2. However, we were intrigued by the stereochemistry obtained when an alkyl substituent was introduced in the allylic position for the reaction performed through metalation (Scheme 3, path A) versus alkynylation of acylsilane (Scheme 3, path B).



Scheme 3.

In the former case, and following our previously described 'metalation–transmetalation' procedure, the allenyl organozinc bromide reagent **10** undergoes a highly diastereoselective cyclization reaction to lead to three contiguous stereogenic center on a cyclopentane ring **11** with total diastereoselection (Scheme 3, path A).[5] In contrast, when **12** was treated with alkynylmagnesium bromide derivatives **5**, two diastereoisomers **13** were first obtained in a 1:1 ratio (as determined by crude NMR on hydrolyzed aliquots). The addition of zinc salt promotes the tandem Zn-Brook rearrangement and Zn-ene-allene cyclization, to give the cyclic isomers **16a**,**b** in good yields, but in a 1:1 ratio (Scheme 3, path B).[10b]

Therefore, we suggest that each diastereoisomer of the allenylzinc bromide **14a** and **14b** (with regard to the allylic stereogenic center), generated through our tandem reaction, leads to its own cyclic product **15a**,**b**, since allenylzinc species are known to be configurationally stable.[11] If indeed each diastereoisomer of **14a**, **b** leads to its own cyclic product, one may assume that the preparation of enantiomerically enriched allenylzinc derivatives would lead to enantiomerically enriched product as described in Scheme 4. Thus, a few important questions were immediately raised:

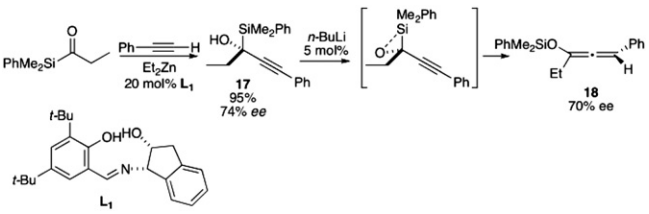
(1) How to prepare enantioenriched propargylsilanol?
(2) Will the Brook rearrangement proceeds with complete transfer of chirality?
(3) What will be the stereochemistry of the stereocenter generated in the reaction?
(4) Will the allenylzinc species remain configurationally stable in these experimental conditions?
(5) Will the carbocyclization always be diastereoselective?

If all these questions could be answered, the diastereo- and enantioselective intramolecular carbometalation through the Zn-ene-allene reaction would now become possible.

Scheme 4.

2. Results and discussion

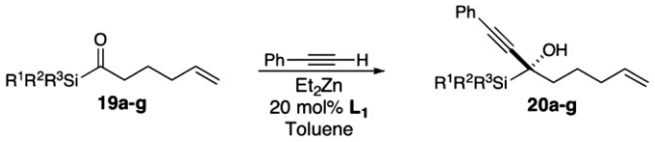
Although the preparation of enantioenriched propargylic alcohols represents a stimulating and dynamic area in organic synthesis,[12] the addition of alkynes to acylsilanes is much less documented and therefore remains a challenging goal. Fortunately, Scheidt has recently reported the preparation of moderately enantioenriched propargylsilane **17** through the catalytic asymmetric alkyne addition to acylsilane using chiral ligand $\mathbf{L_1}$ with 74% enantiomeric excess.[13] This substrate undergoes the Brook rearrangement with a catalytic amount of *n*-BuLi to provide the corresponding enantioenriched allene **18** with minimal erosion of the stereochemical information (Scheme 5).



Scheme 5.

If the reaction described by Scheidt would also be applicable to various ω-ene acylsilanes, a powerful new entry, through asymmetric catalysis, would be opened for the formation of enantioenriched metalated carbocycles. Therefore, we investigated the enantioselectivity of the alkynylation of various ω-ene acylsilanes as described in Table 1, and we found that the nature of the substituents on the silicon atom has a dramatic effect on the enantioselectivity of the reaction. When acylsilane **19a**, possessing three methyl groups, was alkynylated (Table 1, entry 1), the enantiomeric ratio of the corresponding propargylsilanol is only 76:24. A even lower selectivity was obtained when triethylsilane was used (Table 1, entry 2). However, replacement of one methyl by one phenyl group increases the enantiomeric ratio substantially (er 86:14, Table 1, entry 3). The presence of this aromatic ring is essential for good selectivity since its saturated analog (R^3=*c*-C_6H_{11}) or a bulkier group (R^3=*t*-C_4H_9) lead to either lower enantiomeric ratio or almost racemic species in low yield (Table 1, entries 4 and 5, respectively). Interestingly, when two phenyl rings are present, the best selectivity was achieved (Table 1, entry 6) whereas the use of triphenylacylsilane (Table 1, entry 7) leads again to lower selectivity.

Table 1
Effect of substituents on silicon on the enantioselectivity of the alkynylation of acylsilanes **19**

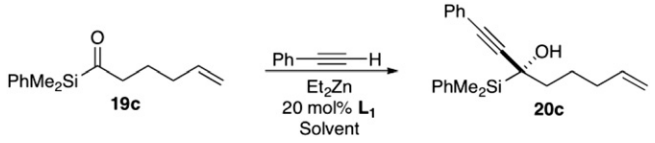


Entry	R^1	R^2	R^3	Pdts	Yield[a] (%)	er[b]
1 (**19a**)	Me	Me	Me	**20a**	96	76:24
2 (**19b**)	Et	Et	Et	**20b**	89	63:37
3 (**19c**)	Me	Me	Ph	**20c**	93	86:14
4 (**19d**)	Me	Me	*c*-C_6H_{11}	**20d**	95	73:27
5 (**19e**)	Me	Me	*t*-Bu	**20e**	55	53:47
6 (**19f**)	Me	Ph	Ph	**20f**	83	88:12
7 (**19g**)	Ph	Ph	Ph	**20g**	51	63:37

[a] Yield determined after purification by column chromatography.
[b] Enantiomeric ratio determined by chiral HPLC (Chiracel AD-H, 5% IPA/hexanes).

Although additional studies are needed to fully understand the effect of substituents on acylsilanes, symmetric (R^1=R^2=R^3) as well as asymmetric with a bulky substituent (R^3=*c*-C_6H_{11} or *t*-Bu) acylsilane lead to low enantiomeric ratios. Good ratios can only be obtained when an aryl group is present on the acylsilane (R^3=Ph). The absolute configuration of **20c** was determined by comparison of the experimental and calculated circular dichroism spectra.[14,15] Aiming to further improve the enantioselectivity of the reaction, several solvents were tested in the alkynylation reaction of acylsilane **19c** as shown in Table 2.

Table 2
Solvent effects on the enantioselectivity of the alkynylation of acylsilane **19c**

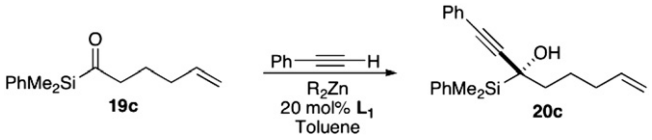


Entry	Solvent	Yield[a] (%)	er[b]
1	Toluene	96	86:14
2	Hexane	85	80:20
3	Et_2O	91	81:19
4	CH_2Cl_2	89	82:18
5	THF	<7	[c]

[a] Yield determined after purification by column chromatography.
[b] Enantiomeric ratio determined by chiral HPLC (Chiracel AD-H, 5% IPA/hexanes).
[c] Not determined.

As can be seen from the results summarized in Table 2, the reaction proceeds efficiently in all cases (except THF) and **20c** is obtained in similar yields and enantioselectivity. Toluene showed slightly better results, and therefore, was used for further optimization. The nature of the dialkylzinc used for the deprotonation of the alkyne has also an effect on the enantioselectivity of the reaction as shown in Table 3.

Table 3
Nature of R_2Zn on the enantioselectivity of alkynylation of the acylsilane **19c**



Entry	R_2Zn	Yield[a] (%)	er[b]
1	Et_2Zn	96	86:14
2	Me_2Zn	53	65:35
3	Bu_2Zn	62	75:25
4	Ph_2Zn	23	68:32
5	*t*-$BuMe_2Si_2Zn$	7	57:43

[a] Yield determined after purification by column chromatography.
[b] Enantiomeric ratio determined by chiral HPLC (Chiracel AD-H, 5% IPA/hexanes).

Diethylzinc (Table 3, entry 1) is by far the best R_2Zn in term of yield and enantiomeric ratio of the desired product. An additional factor that we briefly investigated was the presence of additional metallic salts. For instance, addition of 1 equiv of $ZnBr_2$ should lead, via a Schlenk equilibrium to the alkynyl zinc bromide instead of alkyl alkynyl zinc species and as expected the reaction still proceed in good yield (87%) but racemic adduct was obtained (54:46 er). An additional attempt was to add a lithium salt to form the more reactive zincate species or to use a cocatalyst such as Ti(O-*i*Pr)$_4$; here again the reaction afforded the expected product in good yields but in racemic forms. Finally, we screened a number of chiral ligands (**L_1**–**L_{20}**) for the transformation of **19c** into **20c** (Et_2Zn, toluene) and yields and as well as enantiomeric ratios as summarized in Chart 1.

As shown in Chart 1, while keeping constant indenol as the amino alcohol residue, decent enantioselectivity was only observed when two *tert*-butyl groups were present on the aromatic ring (compare **L_1** with **L_{2-4}**). Keeping now constant the aryl group, various amino alcohols were examined and the best result found so far was with the ligand **L_7** resulting from the condensation of *tert*-leucinol with 3,5-di-*tert*-butyl-2-hydroxybenzaldehyde (compare **L_7** with **$L_{5,6}$** and **$L_{8,9}$**). The nature of the aryl group was also briefly checked with *tert*-leucinol and again, the best enantiomeric ratio was obtained when the two *tert*-butyl groups are present (ligand **L_7** vs **L_{10-12}**). All other variations (**L_{13}**–**L_{20}**) did not improve the enantiomeric ratio.

Although the best enantiomeric ratio obtained is only 90:10 with **L_7**, we did not pursue a deeper investigation of chiral ligands since we were more interested to investigate the stereochemistry of the Zn-Brook rearrangement followed by its Zn-ene-allene carbocyclization. The Brook rearrangement usually proceeds only when a catalytic amount of base is utilized and the typically rapid and essentially irreversible reaction is by protonation of the carbanion by the starting alcohol.[16] Therefore, transfer of chirality into a metalated allenyl species through a stoichiometric amount of base for the Brook rearrangement[17] had no precedent and also drove our curiosity. Indeed, having in hand propargylsilanol **20c**, we then investigated the transfer of chirality in the tandem Zn-Brook rearrangement followed by the Zn-ene-allene carbocyclization reaction as described in Scheme 6.[14]

We were pleased to see that when a solution of Et_2Zn was added to enantioenriched **20c** (er 76:24) in THF and heated at 40 °C for 24 h,[18] the corresponding cyclic product **21** was obtained, after

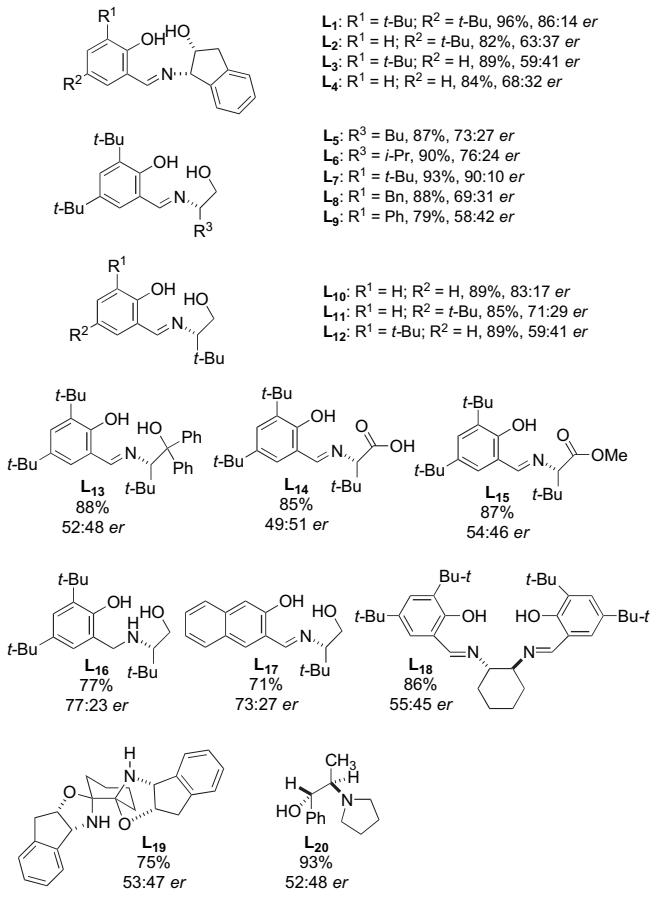
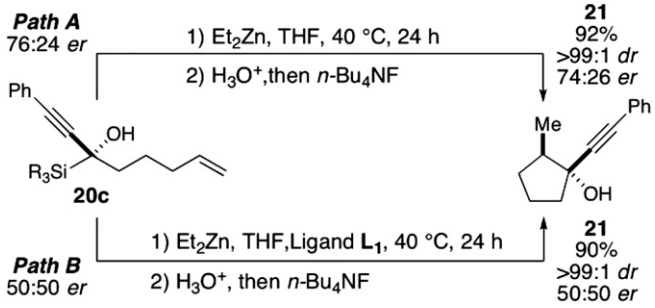


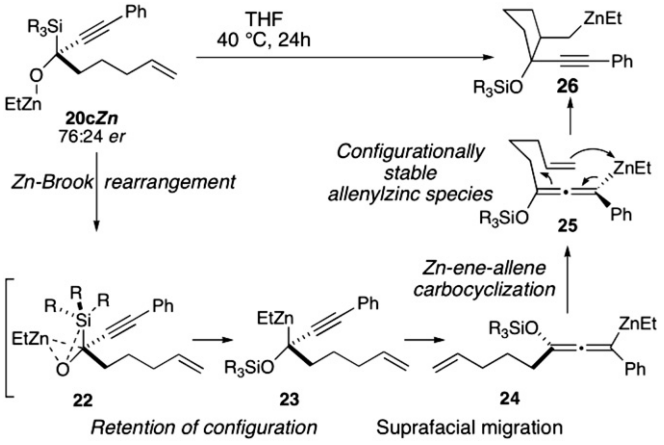
Chart 1.



Scheme 6.

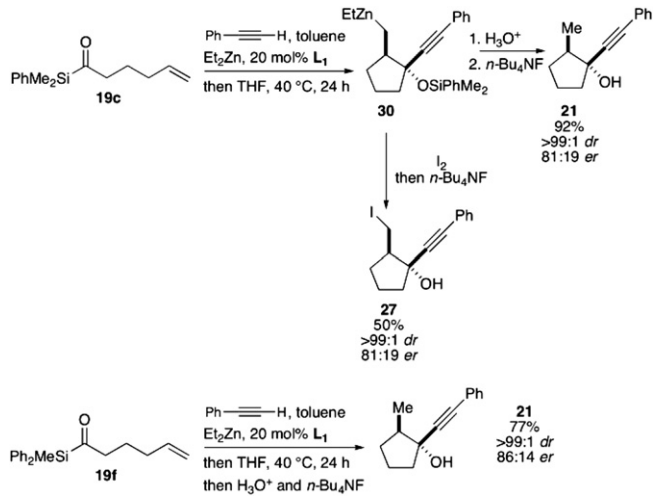
hydrolysis, in excellent yield with a similar enantiomeric ratio (er 74:26) over three consecutive steps (Zn-Brook rearrangement, Zn suprafacial migration, and Zn-ene-allene cyclization, Scheme 6, path A).[19] On the other hand, when racemic **20c** was treated with Et_2Zn in the presence of chiral ligand $\mathbf{L_1}$, only racemic **21** was formed, excluding a possible equilibration of racemic propargyl/allenylzinc into enantiomerically enriched species via interactions with chiral ligand (Scheme 6, path B). The stereochemical outcome of the first rearrangement, namely the 1,2-silyl migration, has been occasionally investigated in the chemistry of organolithium species and occurs with partial inversion of configuration for secondary and tertiary α-silyl benzyl alcohols but with retention (>97%) of configuration for saturated α-silyl alcohols.[20] However, silylalkyl anions were always intercepted rapidly and irreversibly in-situ by using solvents containing water or a protic source.[17] No report on the stereochemistry of the 1,2-Brook rearrangement is available particularly for the formation of a propargylzinc species.

Although more mechanistic investigations are needed to fully explore this rearrangement, the absolute configuration of the starting propargylsilanol **20c** and the final cyclic product **21** (also determined by comparing experimental and theoretical CD spectra)[14] led us to postulate the following mechanistic hypothesis: the oxygen atom of the zinc alcoholate **20cZn** first interacts with the silicon atom to form through the transition state **22**,[21] the Brook product **23**. The zinc countercation occupies the less sterically hindered face, adjacent to the alkyne (Scheme 7). Thus, the zinc-Brook rearrangement leads to the corresponding propargylzinc derivative **23** (possibly only as a transient species), with pure retention of configuration. The second rearrangement in our process, the metalotropic equilibrium with its allenic counterpart **24** occurs via a suprafacial migration leading to the corresponding configurationally stable allenylzinc derivative **24** with pure retention of configuration.[11] The latter then undergoes the last step, a diastereoselective Zn-ene-allene cyclization reaction in which the allenyl metal moiety plays the role of the ene moiety and fixes the cis relationship of the two substituents as described in **25** to give the corresponding alkynyl cyclopentyl methylzinc derivative **26** (Scheme 7). Clearly, this whole sequence (three consecutive steps) proceeds with virtually complete transfer of chirality from **20c** to **26** with the creation of two new stereocenters, including the formation of a quaternary stereocenter.[22]



Scheme 7.

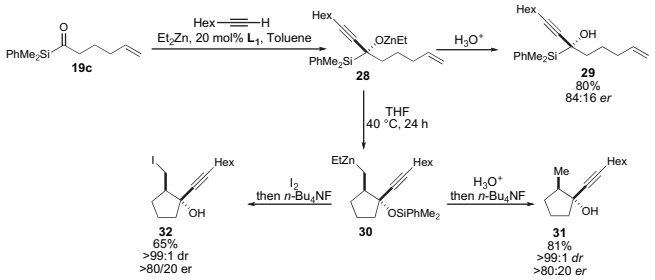
As the alkynylation of the acylsilane, the Brook rearrangement and the carbocyclization involve only zinc species, we were therefore able to perform the entire sequence in a single-pot operation as described in Scheme 8, via asymmetric catalysis. When acylsilane



Scheme 8.

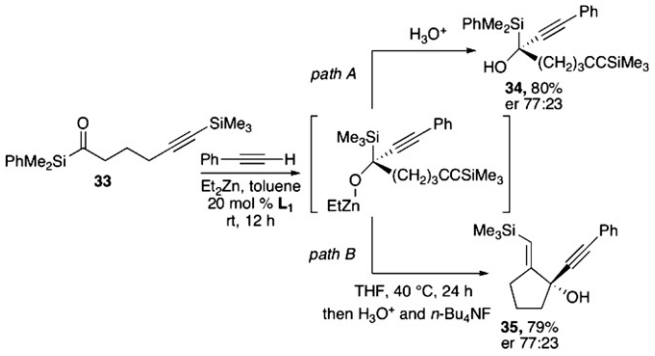
19c was added to phenylacetylene in the presence of Et_2Zn and 20 mol % of chiral ligand $\mathbf{L_1}$, as shown in Scheme 8, the corresponding cyclopentanol **21** was obtained in excellent isolated yield as a unique diastereoisomer with an almost complete transfer of chirality after hydrolysis. The formation of a discrete organometallic species after carbocyclization was checked by iodinolysis (formation of **27**).

The same behavior was found when acylsilane **19f** was treated with phenylacetylene. The enantiomeric ratio determined after the alkynylation reaction is practically the same as the one obtained for the cyclic product **21** (88:12 for propargylsilanol **20f** versus 86:14 er for **21**, Scheme 8). Similarly, when acylsilane **19c** was treated with 1-octyne, the enantiomeric ratio of the cyclic products **31** and **32**, after hydrolysis and iodinolysis, respectively, are in the same range as those of the hydrolyzed addition product **29** (Scheme 9).[23]



Scheme 9.

The same principle could be extended to the enantioselective Zn-yne-allene cyclization as described in Scheme 10. The addition of phenylacetylene to the new acylsilane **33** possessing an electrophilic alkynylsilane moiety led to the corresponding propargylsilanol **34**, after hydrolysis, in excellent yield with an enantiomeric ratio of 77:23 (path A, Scheme 10). By heating the reaction mixture at 40 °C in THF for 24 h before hydrolysis, the cyclic product **35**, resulting from the Brook rearrangement followed by suprafacial migration of the zinc along the carbon chain of the alkyne and then the Zn-yne-allene carbocyclization, was obtained in 79% yield with a complete transfer of chirality (77:23 er) and as a unique *E*-geometrical isomer.



Scheme 10.

3. Conclusions

In summary, the catalytic enantioselective alkynylation of an acylsilane followed by a zinc-promoted Brook rearrangement and finally the Zn-ene-allene or Zn-yne-allene cyclization represents a very efficient and powerful entry to enantiomerically enriched carbocycles with formation of synthetically challenging quaternary stereocenters. Three new bonds are generated in a single-pot operation. One of the most remarkable features of this enantioselective intramolecular carbometalation reaction are the highly efficient transfer of chirality in the formation of the organometallic product during the Zn-Brook rearrangement. Currently, our efforts are directed toward expanding this concept to various different and challenging substrates.

4. Experimental section

4.1. General

Experiments involving organometallics were carried out under a positive pressure of argon. All glassware were oven dried at 150 °C overnight and assembled quickly while hot under a stream of argon. Liquid nitrogen was used as a cryogenic fluid and all indicated temperatures, unless otherwise stated, refer to internal ones. Ether and THF were distilled from sodium benzophenone ketyl. NMR spectra were recorded in $CDCl_3$. Chemical shifts are reported in part per million (ppm) relative to tetramethylsilane (TMS) as an internal standard (0.1%) in ^1H NMR spectra. In ^{13}C NMR spectra, $CDCl_3$ (δ=77 ppm) was used as a reference.

Starting materials were prepared by standard procedure from literature.[24]

4.1.1. 1-Trimethylsilyl-hex-5-en-1-one[14] ***19a***. Compound **19a** was prepared according to the standard procedure.[24] After purification by column chromatography, 1.08 g (80%) of **19a** was obtained as a colorless liquid. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.16 (s, 9H), 1.59 (quint, J=7.5 Hz, 2H), 1.99 (q, J=7.0 Hz, 2H), 2.57 (t, J=7.2 Hz, 2H), 4.91–4.98 (m, 2H), 5.69–5.74 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): −3.2, 21.1, 33.2, 47.5, 115.0, 138.1, 248.3; FTIR (thin film): 912, 997, 1079, 1091, 1162, 1249, 1351, 1411, 1443, 1642, 2856, 2927, 2956 cm^{-1}.

4.1.2. 1-Triethylsilyl-hex-5-en-1-one[14] ***19b***. Compound **19b** was prepared according to the standard procedure.[24] After purification by column chromatography, the expected acylsilane **19b** was obtained in 91% yield as a colorless liquid. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.73 (q, J=14 Hz, 6H), 0.95 (t, J=14.5 Hz, 9H), 1.63 (quint, J=7.5 Hz, 2H), 2.02 (q, J=7.0 Hz, 2H), 2.56 (t, J=7.2 Hz, 2H), 4.93–5.02 (m, 2H), 5.69–5.79 (m, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 5.8, 7.2, 22.1, 33.1, 47.5, 115.0, 138.1, 248.5; FTIR (thin film): 912, 997, 1079, 1091, 1162, 1249, 1351, 1411, 1443, 1642, 2856, 2927, 2956 cm^{-1}.

4.1.3. 1-Dimethyl(phenyl)silyl-hex-5-en-1-one[14] ***19c***. Compound **19c** was prepared according to the standard procedure.[24] After purification by column chromatography, the expected acylsilane **19c** was obtained in 81% yield as an yellow liquid. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.52 (s, 6H), 1.60 (dquint, J_1=7.2 Hz, J_2=1.2 Hz, 2H), 1.97 (dq, J_1=7.4 Hz, J_2=0.9 Hz, 2H), 2.61 (dt, J_1=0.9 Hz, J_2=7.2 Hz, 2H), 4.91–4.97 (m, 2H), 5.65–5.75 (m, 1H), 7.35–7.42 (m, 3H), 7.57–7.59 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): −4.9, 21.0, 32.9, 47.7, 114.8, 128.0, 129.7, 132.8, 133.8, 137.9, 245.8; FTIR (thin film): 912, 998, 1026, 1062, 1114, 1253, 1428, 1642, 2939, 2958, 3071 cm^{-1}.

4.1.4. 1-Dimethyl(cyclohexyl)silyl-hex-5-en-1-one[14] ***19d***. Compound **19d** was prepared according to the standard procedure.[24] After purification by column chromatography, the expected acylsilane **19d** was obtained in 75% yield as a colorless liquid. ^1H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.13 (s, 6H), 0.87–0.88 (m, 2H), 1.07–1.24 (m, 6H), 1.58–1.71 (m, 5H), 2.01 (q, J=7.0 Hz, 2H), 2.57 (t, J=7.2 Hz, 2H), 4.93–5.02 (m, 2H), 5.70–5.79 (m, 1H); ^{13}C NMR ($CDCl_3$,125 MHz) δ (ppm): −3.2, 19.4, 21.1, 25.5, 27.2, 28.6, 33.2, 47.5, 115.0, 138.1, 248.3; FTIR (thin film): 910, 999, 1079, 1089, 1162, 1249, 1351, 1411, 1443, 1642, 2854, 2925, 2956 cm^{-1}.

4.1.5. 1-Dimethyl(tert-butyl)silyl-hex-5-en-1-one[14] ***19e***. Compound **19e** was prepared according to the standard procedure.[24] After

purification by column chromatography, the expected acylsilane **19e** was obtained in 49% yield as a colorless liquid. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.09 (s, 9H), 0.84 (s, 9H), 1.52 (quint, J=7.5 Hz, 2H), 1.93 (q, J=5.1 Hz, 2H), 2.51 (t, J=7.7 Hz, 2H), 4.84–4.91 (m, 2H), 5.62–5.68 (m, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): −7.2, 16.3, 20.7, 26.2, 33.0, 49, 114.8, 138.0, 246.7; FTIR (thin film): 912, 998, 1251, 1363, 1405, 1467, 1641, 2859, 2887, 2898, 2931, 2952 cm^{-1}.

4.1.6. 1-Methyl(diphenyl)silyl-hex-5-en-1-one[14] ***19f***. Compound **19f** was prepared according to the standard procedure.[24] After purification by column chromatography, the expected acylsilane **19f** was obtained in 79% yield as a yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.69 (s, 3H), 1.52 (quint, J=7.2 Hz, 2H), 1.84 (q, J_1=1.2 Hz, J_2=7.2 Hz, 2H), 2.60 (dt, J_1=3.4 Hz, J_2=7.1 Hz, 2H), 4.78–4.84 (m, 2H), 5.52–5.57 (m, 1H), 7.26–7.29 (m, 6H), 7.51–7.54 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): −5.6, 20.9, 32.7, 48.5, 114.7, 127.9, 129.8, 129.8, 134.7, 137.7, 243.6; FTIR (thin film): 913, 997, 1112, 1253, 1429, 1642, 2931, 3050, 3071 cm^{-1}.

4.1.7. 1-Triphenylsilyl-hex-5-en-1-one[14] ***19g***. Compound **19g** was prepared according to the standard procedure.[24] After purification by column chromatography, the expected acylsilane **19g** was obtained in 43% yield as yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.55 (quint, J=7.2 Hz, 2H), 1.89 (q, J_1=1.2 Hz, J_2=7.2 Hz, 2H), 2.60 (dt, J_1=3.4 Hz, J_2=7.1 Hz, 2H), 4.78–4.84 (m, 2H), 5.52–5.57 (m, 1H), 7.23–7.38 (m, 10H), 7.51–7.54 (m, 5H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 20.5, 32.7, 48.5, 114.7, 127.9, 129.8, 129.8, 134.7, 137.7, 243.6; FTIR (thin film): 918, 997, 1112, 1253, 1427, 1642, 2935, 3050, 3071 cm^{-1}.

4.1.8. 1-Trimethylsilyl-hex-(6-trimethylsilyl)-5-yn-1-one[14] ***33***. Compound **33** was prepared according to the standard procedure.[24] After purification by column chromatography, **33** was obtained in 77% yield as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.03 (s, 9H), 0.09 (s, 9H), 1.60 (quint, J=6.0 Hz, 2H), 2.11 (t, J=6.1 Hz, 2H), 2.64 (t, J=5.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): −3.4, −3.3, 0.0, 19.0, 20.7, 46.4, 85.0, 106.4, 247.2; FTIR (thin film): 911, 1044, 1248, 1351, 1407, 1430, 1645, 2173, 2900, 2957 cm^{-1}.

4.2. Preparation of enantiomerically enriched propargylsilanol derivatives

To a flame-dried round bottom flask charged with alkyne (1.0 mmol) in toluene (2 mL) was added diethylzinc (1.0 mmol, 1.5 M in toluene). The solution was first stirred at rt for 1 h, and then chiral ligand (0.100 mmol) was added in toluene (1 mL). After the solution had been stirred for an additional 1 h, acylsilane (0.50 mmol) dissolved in toluene (1 mL) was added at room temperature. The yellow solution was stirred until complete consumption of acylsilane (8–12 h, followed by TLC analysis with a 10% EtOAc/hexane eluent) at room temperature. The reaction was then quenched at room temperature with a saturated aqueous solution of NH_4Cl and extracted with Et_2O (3×10 mL). The organic solution was washed with brine (10 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated to give the unpurified propargylsilane. The product was purified by flash chromatography (5% EtOAc/hexanes).

4.2.1. (R)-3-Trimethylsilyl-1-phenyl-oct-7-en-1-yn-3-ol ***20a***. Compound **20a** was prepared according to the general procedure using **19a** (85 mg, 0.50 mmol), phenylacetylene (0.11 mL, 1.0 mmol), $ZnEt_2$ (0.7 mL, 1.0 mmol), and ligand $\mathbf{L_1}$ (36.5 mg, 0.100 mmol) to afford 130.2 mg of **20a** (96%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.17 (s, 9H), 1.67–1.75 (m, 4H), 2.12–2.14 (m, 2H), 4.94–5.06 (m, 2H), 5.79–5.88 (m, 1H), 7.27–7.29 (m, 3H), 7.37–7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): −4.2, 23.1, 33.9, 36.8, 64.9, 87.6, 91.8, 114.6, 123.4, 127.9, 128.2, 131.5, 138.6; $[\alpha]_D^{25}$ +13.6 (CH_2Cl_2, c 0.9, er=76:24). The enantiomeric ratio was measured by chiral HPLC (Chiracel AD-H, 3% IPA/hexanes, Rt_1=8.12, Rt_2=14.02).

4.2.2. (R)-3-Triethylsilyl-1-phenyl-oct-7-en-1-yn-3-ol ***20b***. Compound **20b** was prepared according to the general procedure using **19b** (106 mg, 0.50 mmol), phenylacetylene (0.11 mL, 1.0 mmol), $ZnEt_2$ (0.7 mL, 1.0 mmol), and ligand $\mathbf{L_1}$ (36.5 mg, 0.100 mmol) to afford 139.8 mg of **20b** (89%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.75 (q, J=7.5 Hz, 6H), 1.03 (t, J=6.9 Hz, 9H), 1.69 (br s, 1H), 1.73–1.75 (m, 4H), 2.11–2.14 (m, 2H), 4.94–5.00 (m, 2H), 5.79–5.86 (m, 1H), 7.24–7.29 (m, 3H), 7.35–7.36 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 2.6, 8.1, 22.7, 33.8, 37.0, 65.2, 89.2, 91.7, 115.6, 123.1, 128.3, 128.4, 131.4, 139.1; $[\alpha]_D^{25}$ +18.6 (CH_2Cl_2, c 1.1, er=63:37). The enantiomeric ratio was measured by chiral HPLC (Chiracel AD-H, 5% IPA/hexanes, Rt_1=6.82, Rt_2=16.72).

4.2.3. (R)-3-Dimethyl(phenyl)silyl-1-phenyl-oct-7-en-1-yn-3-ol ***20c***. Compound **20c** was prepared according to the general procedure using **19c** (116 mg, 0.50 mmol), phenylacetylene (0.11 mL, 1.0 mmol), $ZnEt_2$ (0.7 mL, 1.0 mmol), and ligand $\mathbf{L_1}$ (36.5 mg, 0.100 mmol) to afford 157.8 mg (94%) of **20c** as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.52 (s, 6H), 1.67–1.75 (m, 4H), 1.99 (br s, 1H), 2.08–2.10 (m, 2H), 4.93–5.05 (m, 2H), 5.81–5.83 (m, 1H), 7.30–7.32 (m, 3H), 7.38–7.41 (m, 5H), 7.69–7.71 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): −5.9, −5.6, 23.1, 33.8, 36.9, 64.8, 88.1, 91.8, 114.5, 123.3, 127.7, 127.9, 128.2, 129.6, 131.4, 134.7, 135.2, 138.6; $[\alpha]_D^{25}$ +23.1 (CH_2Cl_2, c 0.9, er=86:14). The enantiomeric ratio was measured by chiral HPLC (Chiracel AD-H, 5% IPA/hexanes, Rt_1=5.70, Rt_2=14.40).

4.2.4. (R)-3-Dimethyl(cyclohexyl)silyl-1-phenyl-oct-7-en-1-yn-3-ol ***20d***. Compound **20d** was prepared according to the general procedure using **19d** (108 mg, 0.50 mmol), phenylacetylene (0.11 mL, 1.0 mmol), $ZnEt_2$ (0.7 mL, 1.0 mmol), and ligand $\mathbf{L_1}$ (36.5 mg, 0.100 mmol) to afford 187.1 mg of **20d** (95%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.10 (s, 6H), 0.81 (m, 4H), 0.94 (m, 4H), 1.21 (m, 4H), 1.72–1.75 (m, 4H), 2.11–2.13 (m, 2H), 4.93–5.06 (m, 2H), 5.79–5.85 (m, 1H), 7.23–7.29 (m, 3H), 7.35–7.38 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): −4.2, 18.5, 23.1, 25.5, 27.6, 28.6, 33.8, 36.8, 63.2, 89.2, 91.0, 114.6, 123.1, 128.3, 128.4, 131.0, 139.1; $[\alpha]_D^{25}$ +19.1 (CH_2Cl_2, c 1.1, er=73:27). The enantiomeric ratio was measured by chiral HPLC (Chiracel AD-H, 5% IPA/hexanes, Rt_1=6.87, Rt_2=15.62).

4.2.5. (R)-3-Dimethyl(tert-butyl)silyl-1-pheny-loct-7-en-1-yn-3-ol ***20e***. Compound **20e** was prepared according to the general procedure using **19e** (106 mg, 0.50 mmol), phenylacetylene (0.11 mL, 1.0 mmol), $ZnEt_2$ (0.7 mL, 1.0 mmol), and ligand $\mathbf{L_1}$ (36.5 mg, 0.100 mmol) to afford 86.4 mg (55%) of **20e** as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.13 (s, 3H), 0.14 (s, 3H), 1.05 (s, 9H), 1.63 (s, 1H), 1.71–1.81 (m, 4H), 2.11–2.14 (m, 2H), 4.94–5.06 (m, 2H), 5.79–5.88 (m, 1H), 7.27–7.29 (m, 3H), 7.36–7.37 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): −7.6, −7.3, 1.0, 22.7, 27.8, 33.9, 38.0, 65.4, 87.9, 92.7, 114.6, 123.5, 127.9, 128.3, 131.3, 138.7; $[\alpha]_D^{25}$ 0.0 (CH_2Cl_2, c 1.1, er=53:47). The enantiomeric ratio was measured by chiral HPLC (Chiracel AD-H, 5% IPA/hexanes, Rt_1=6.64, Rt_2=8.81).

4.2.6. (R)-3-Methyl(diphenyl)silyl-1-phenyl-oct-7-en-1-yn-3-ol ***20f***. Compound **20f** was prepared according to the general procedure using **19f** (146 mg, 0.50 mmol), phenylacetylene (0.11 mL, 1.0 mmol), $ZnEt_2$ (0.7 mL, 1.0 mmol), and ligand $\mathbf{L_1}$ (36.5 mg, 0.100 mmol) to afford 154.5 mg (78%) of **20f** as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.75 (s, 3H), 1.54 (br s, 1H), 1.71–1.82 (m, 4H), 2.00–2.05 (m, 2H), 4.88–4.99 (m, 2H), 5.72–5.81 (m, 1H), 7.28–7.40 (m, 11H), 7.76–7.77 (m, 4H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ

(ppm): −6.2, 23.0, 33.8, 37.3, 64.9, 88.9, 92.0, 114.5, 123.2, 127.8, 127.8, 128.1, 128.2, 129.7, 129.8, 131.4, 133.6, 133.9, 135.6, 135.6, 138.6; $[\alpha]_D^{25}$ +28.0 (CH_2Cl_2, *c* 1, er=88:12). The enantiomeric ratio was measured by chiral HPLC (Chiracel AD-H, 5% IPA/hexanes, Rt_1=7.78, Rt_2=28.41).

4.2.7. (R)-3-Triphenylsilyl-1-pheny-loct-7-en-1-yn-3-ol ***20g***. Compound **20g** was prepared according to the general procedure using **19g** (165 mg, 0.50 mmol), phenylacetylene (0.11 mL, 1.0 mmol), $ZnEt_2$ (0.7 mL, 1.0 mmol), and ligand $\mathbf{L_1}$ (36.5 mg, 0.100 mmol) to afford 114.5 mg of **20g** (51%) as a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.71–1.75 (m, 4H), 2.01–2.04 (m, 2H), 4.83–4.96 (m, 2H), 5.71–5.81 (m, 1H), 7.18–7.56 (m, 20H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 23.0, 33.9, 37.2, 65.2, 89.2, 91.9, 114.6, 123.1, 127.7, 127.8, 128.2, 128.3, 128.4, 129.7, 129.9, 131.0, 133.5, 133.8, 136.0, 136.3, 139.1; $[\alpha]_D^{25}$ +29.4 (CH_2Cl_2, *c* 1.1, er=63:37). The enantiomeric ratio was measured by chiral HPLC (Chiracel AD-H, 5% IPA/hexanes, Rt_1=7.91, Rt_2=17.18).

4.2.8. (R)-3-Dimethyl(phenyl)silyl-1-phenyl-oct-7-en-1-yn-3-ol ***29***. Compound **29** was prepared according to the general procedure using **19c** (116 mg, 0.50 mmol), 1-octyne (0.13 mL, 1.0 mmol), $ZnEt_2$ (0.7 mL, 1.0 mmol), and ligand $\mathbf{L_1}$ (36.5 mg, 0.100 mmol) to afford 136.9 mg (80%) of **29** as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.40 (s, 6H), 0.88 (t, *J*=7.1 Hz, 3H), 1.23–1.83 (m, 10H), 2.00–2.19 (m, 4H), 2.21 (t, *J*=6.9 Hz, 2H), 4.88–4.99 (m, 2H), 5.70–5.81 (m, 1H), 7.34–7.67 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): −5.8, −5.6, 14.1, 19.0, 22.6, 28.6, 28.9, 29.7, 31.4, 33.9, 37.1, 60.1, 82.3, 88.7, 114.4, 127.6, 129.4, 130.9, 134.7, 138.8; $[\alpha]_D^{25}$ +23.1 (CH_2Cl_2, *c* 0.9, er=86:14). Enantiomeric ratio was measured by chiral HPLC (Chiracel AD-H, 5% IPA/hexanes, Rt_1=5.70, Rt_2=14.40).

4.2.9. (R)-3-Trimethylsilyl-1-phenyl-oct-7-yn-8-trimethylsilyl-1-yn-3-ol ***34***. Compound **34** was prepared according to general procedure using **33** (120 mg, 0.50 mmol), phenylacetylene (0.11 mL, 1.0 mmol), $ZnEt_2$ (0.7 mL, 1.0 mmol), and ligand $\mathbf{L_1}$ (36.5 mg, 0.100 mmol) to afford 161.7 mg (80%) of **34** as a colorless oil. ^{1}H NMR ($CDCl_3$, 500 MHz) δ (ppm): 0.13 (s, 9H), 0.14 (s, 9H), 1.66 (br s, 1H), 1.80–1.88 (m, 4H), 2.32 (dt, J_1=6.6 Hz, J_2=1.5 Hz, 2H), 7.27–7.29 (m, 3H), 7.37–7.39 (m, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): −4.2, 0.1, 20.0, 23.2, 36.4, 64.7, 85.0, 87.7, 91.6, 107.2, 123.3, 127.9, 128.2, 131.5; $[\alpha]_D^{25}$ −21.0 (CH_2Cl_2, *c* 1, er=23:77). The enantiomeric ratio was measured by chiral HPLC (Chiracel AD-H, 5% IPA/hexanes, Rt_1=4.49, Rt_2=5.21).

4.3. General procedure for the enantioselective tandem Zn-Brook rearrangement/Zn-ene-allene carbocyclization reaction

To a flame-dried round bottom flask charged with alkyne (1.0 mmol) in toluene (2 mL) was added diethylzinc (1.0 mmol, 1.5 M in toluene). The solution was first stirred at rt for 1 h, and then ligand $\mathbf{L_1}$ (0.100 mmol) was added in toluene (1 mL). After the solution had been stirred for an additional 1 h, acylsilane (0.50 mmol) dissolved in toluene (1 mL) was added at room temperature. The yellow solution was stirred until complete consumption of acylsilane (8–12 h, followed by TLC analysis with a 10% EtOAc/hexane eluent) at room temperature. Then, THF (five times the volume of toluene) was added and the reaction mixture was stirred at 40 °C for 24 h. The reaction was then quenched with an aqueous saturated solution of NH_4Cl and extracted with Et_2O (3×10 mL). The solution was concentrated to give the unpurified cyclic product, which was further desilylated. To a solution of the corresponding silylether in THF (10 mL) at room temperature was added a 1 M solution of *n*-Bu_4NF (1.05 equiv). When the reaction was over the crude was concentrated under reduced pressure. Then, brine was added and the aqueous phase was extracted five times with Et_2O. Next, the combined organic phases were washed once with brine and dried over $MgSO_4$.

4.3.1. (1R,2R)-2-Methyl-1-(phenylethynyl)-cyclopentanol ***21***. Compound **21** was prepared according to the general procedure using **19c** and compared with literature data:[14] (116 mg, 0.50 mmol), phenylacetylene (0.11 mL, 1.0 mmol), $ZnEt_2$ (0.7 mL, 1.0 mmol), ligand $\mathbf{L_1}$ (36.5 mg, 0.100 mmol). After purification by column chromatography, 92.1 mg (92%) of product (*R*,*R*)-**21** was obtained as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.10 (d, *J*=6.6 Hz, 3H), 1.40–1.43 (m, 1H), 1.56 (br s, 1H), 1.73–1.78 (m, 2H), 1.96–2.16 (m, 4H), 7.27–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 16.5, 20.6, 31.2, 40.9, 46.1, 78.9, 85.9, 90.6, 122.9, 128.2, 128.2, 131.6. $[\alpha]_D^{25}$ +8.4 (CH_2Cl_2, *c* 1, er=81:19). The enantiomeric ratio was measured by chiral HPLC (Chiracel AD-H, 5% IPA/hexanes, Rt_1=13.35, Rt_2=14.04).

4.3.2. (1R,2R)-2-Iodomethyl-1-(phenylethynyl)-cyclopentanol ***27***. Compound **27** was prepared according to the general procedure using **19c** and compared with literature data:[14] (116 mg, 0.50 mmol), phenylacetylene (0.11 mL, 1.0 mmol), $ZnEt_2$ (0.7 mL, 1.0 mmol), ligand $\mathbf{L_1}$ (36.5 mg, 0.100 mmol), and I_2 (6 equiv) was added at −30 °C in 10 ml of THF. The reaction was warmed to room temperature, stirred for an additional 2 h before the hydrolysis and further treatment are done as usual to afford 81.7 mg (50%) of **27** as a yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.65–1.71 (m, 2H), 1.92–1.96 (m, 1H), 2.08–2.12 (m, 2H), 2.20 (t, *J*=7.1 Hz, 2H), 2.28–2.30 (m, 1H), 3.08 (t, *J*=9.3 Hz, 1H), 3.47 (dd, J_1=9.5 Hz, J_2=5.9 Hz, 1H), 7.29–7.43 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm): 7.7, 20.6, 31.2, 40.6, 52.3, 75.9, 83.9, 92.6, 122.9, 128.2, 128.4.

4.3.3. (1R,2R)-2-Methyl-1-(2-octynyl)-cyclopentanol ***31***. Compound **31** was prepared according to the general procedure using **19c** and compared with literature data:[14] (116 mg, 0.50 mmol), 1-octyne (0.15 mL, 1.0 mmol), $ZnEt_2$ (0.7 mL, 1.0 mmol), ligand $\mathbf{L_1}$ (36.5 mg, 0.100 mmol). After purification by column chromatography, 94.8 mg (91%) of product (*R*,*R*)-**31** was obtained as a colorless liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.83–0.88 (d, *J*=6.8 Hz, 3H), 1.00 (d, *J*=6.6 Hz, 3H), 1.23–1.45 (m, 8H), 1.45–1.48 (m, 2H), 1.66–1.69 (m, 2H), 1.85–2.05 (m, 4H), 2.21 (t, *J*=6.9 Hz, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 14.0, 16.4, 18.7, 20.4, 22.5, 28.5, 28.8, 31.0, 31.3, 41.0, 45.7, 78.6, 81.5, 114.5. $[\alpha]_D^{25}$ +4.2 (CH_2Cl_2, *c* 0.8). Both enantiomers were not fully separated by chiral HPLC on Chiracel AD-H column. The enantiomeric ratio was deduced from the reaction with iodine.

4.3.4. (1R,2R)-2-Iodomethyl-1-(2-octynyl)-cyclopentanol ***32***. Compound **32** was prepared according to the general procedure using **19c** and compared with literature data:[14] (116 mg, 0.50 mmol), 1-octyne (0.15 mL, 1.0 mmol), $ZnEt_2$ (0.7 mL, 1.0 mmol), ligand $\mathbf{L_1}$ (36.5 mg, 0.100 mmol), and I_2 (6 equiv) was added at −30 °C in 10 ml of THF. The reaction was warmed to room temperature, stirred for an additional 2 h before the hydrolysis and further treatment were done as usual to afford 108.6 mg (65%) of **32** as a yellow liquid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 0.88 (t, *J*=6.8 Hz, 3H), 1.23–1.31 (m, 5H), 1.34–1.40 (m, 3H), 1.47–1.55 (m, 2H), 1.65–1.70 (m, 2H), 1.92–1.96 (m, 1H), 2.08–2.12 (m, 2H), 2.20 (t, *J*=7.1 Hz, 2H), 2.28–2.30 (m, 1H), 3.08 (t, *J*=9.3 Hz, 1H), 3.45 (dd, J_1=9.5 Hz, J_2=5.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ (ppm): 7.6, 14.1, 18.7, 19.7, 22.6, 28.5, 28.6, 31.2, 31.3, 42.5, 53.1, 77.6, 80.0, 87.0; $[\alpha]_D^{25}$ +8.0 (CH_2Cl_2, *c* 0.8, er>77:23). The enantiomeric ratio was measured by chiral HPLC (Chiracel AD-H, 4% IPA/hexanes, Rt_1=14.90, Rt_2=15.37). In this case, the two enantiomers were only partially separated.

4.3.5. (1R,2E)-2-(Trimethylsilylmethylidene)-1-(phenylethynyl)-cyclopentanol ***35***. Compound **35** is prepared according to general

procedure **33** and compared with literature data:[14] (120 mg, 0.50 mmol), phenylacetylene (0.11 mL, 1.0 mmol), $ZnEt_2$ (0.7 mL, 1.0 mmol), ligand $\mathbf{L_1}$ (36.5 mg, 0.100 mmol). After purification by column chromatography, 105.0 mg (79%) of product (*R*)-**35** was obtained as a colorless liquid. ^1H NMR ($CDCl_3$, 300 MHz) δ (ppm): 1.56 (s, 1H), 1.70–1.78 (m, 2H), 1.91–2.21 (m, 4H), 5.96 (t, J=2.6 Hz, 1H), 7.27–7.42 (m, 5H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): −0.7, 20.6, 29.7, 40.9, 78.9, 85.9, 90.6, 122.3, 122.9, 128.2, 128.2, 163.0. $[\alpha]_D^{25}$ −24.7 (CH_2Cl_2, *c* 1, er=23:77). Enantiomeric ratio was measured by chiral HPLC (Chiracel AD-H, 3% IPA/hexanes, Rt_1=12.73, Rt_2=14.44).

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