On conformational and configurational aspects of molecular motors

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Chapter 2:

ymmetric synthesis of first generation molecular motors based on indanones.

A general enantioselective route to first generation molecular motors based on indanone precursors is described. Methoxy functionalized indanones could be prepared via a polyphosphoric acid (PPA) mediated reaction of which the regioselectivity could be controlled by the P_2O_5 content of the PPA employed. An enantioselective protonation of the silyl enol ethers of indanones by an Au(I)BINAP complex sets the stage for a diastereoselective McMurry coupling to give access to various functionalized overcrowded alkenes in good yields and good to excellent enantiomeric excess values.

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2.1 Introduction

Light-driven molecular motors have been used in functional molecular systems either as unidirectional rotors or as chiral multi-state switches. Noteworthy examples of the latter include their use as photoswitchable catalysts,[1] stereoselective anion binders[2] or as switchable inducers in chirality amplification processes.[3] Especially the first generation molecular motor with a xylene core (Figure 1c), has been a prominent building block for functional molecular systems.[4] This compound, developed in 2008 and sometimes referred to as Mike's motor, benefits from a short synthesis, good photostationary state (PSS) ratios and a high thermal stability of the unstable *cis* isomer.[5] These characteristics make this compound particularly suitable as chiral multi-state switch.

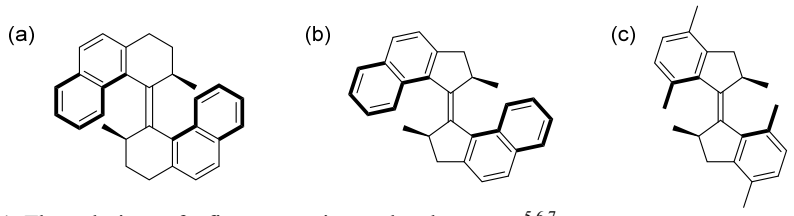
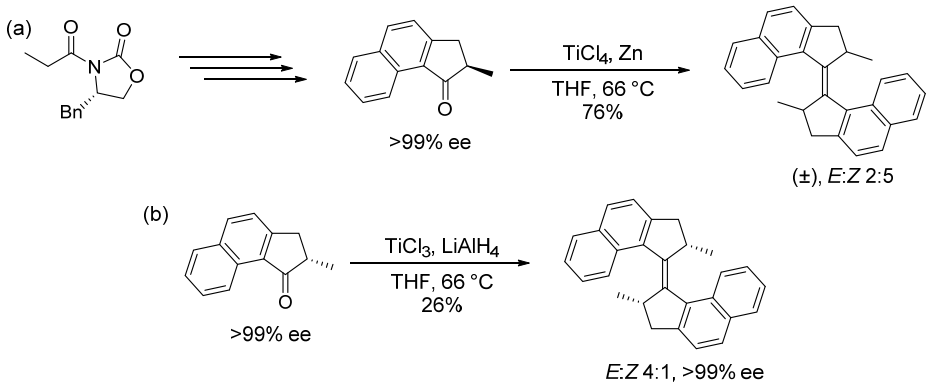


Figure 1: Three designs of a first generation molecular motor.[5,6,7]

Chiral HPLC separations are normally used to obtain first generation molecular motors enantiomerically pure, as the asymmetric synthesis of first generation molecular motors proved to be problematic in the past. Ter Wiel et al. found in the synthesis that the conditions of the McMurry reaction, the key step to form the sterically hindered alkene, leads to complete racemization of the starting material (Scheme 1).[7] In 2005, however, Harada et al. reported on the use of $TiCl_3$ in combination with $LiAlH_4$, allowing access to (unfunctionalized) first generation molecular motors as single enantiomers, albeit in a lower yield.[8]

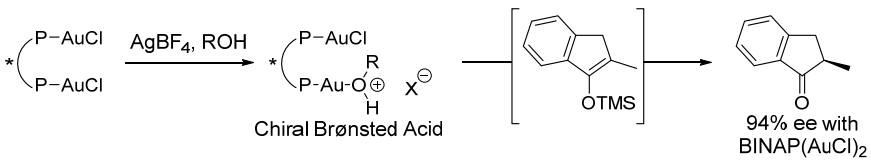


Scheme 1: (a) Loss of stereochemical integrity during the McMurry reaction (b) McMurry reaction proceeding with retention of configuration.[8]

Considering that the development of functional systems based on molecular motors would greatly benefit from a simple method to access these building blocks and knowing that these compounds can be obtained via a McMurry coupling without loss of optical purity, the goal was set to develop a short synthesis of first generation xylene motors with different substitution patterns.

In order to accomplish this objective, a practical enantioselective synthesis of the precursor indanones was required. The enantioselective protonation of enol ethers seemed a promising strategy, as it is widely applicable and it does not necessitate the development of new synthetic routes to ketones of which only the racemic synthesis is known.[9] Especially the gold catalyzed asymmetric protonation of silyl enol ethers (Scheme 2), developed by Toste et al. showed great promise with respect to the goal of this chapter as it was shown that this procedure can be applied for the enantioselective synthesis of 2-methyl-1-indanone.[10]

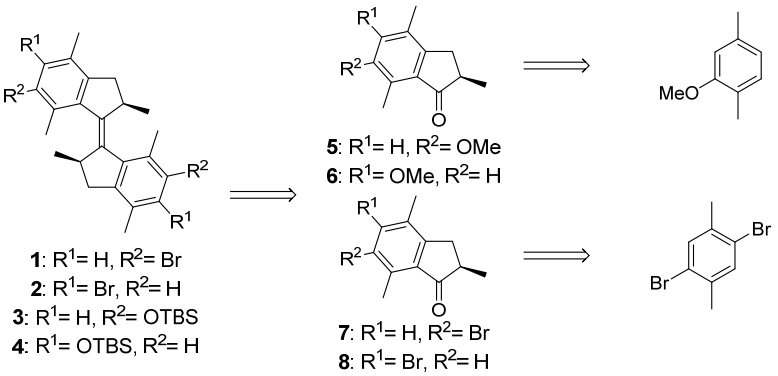
In this chapter, the asymmetric synthesis of various functionalized xylene first generation molecular motors is explored. Key questions which will be addressed are how to synthesize functionalized indanones, how general is Toste's methodology and what are the best conditions for the McMurry reaction in the synthesis of overcrowded alkenes.



Scheme 2: Gold catalyzed enantioselective protonation of silyl enol ethers.[10]

2.2 Results and Discussion

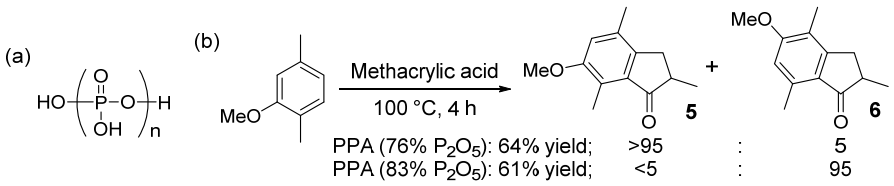
The retrosynthetic analysis of the target structures **1**-**4** is depicted in scheme 3.



Scheme 3: Target structures **1**-**4**.

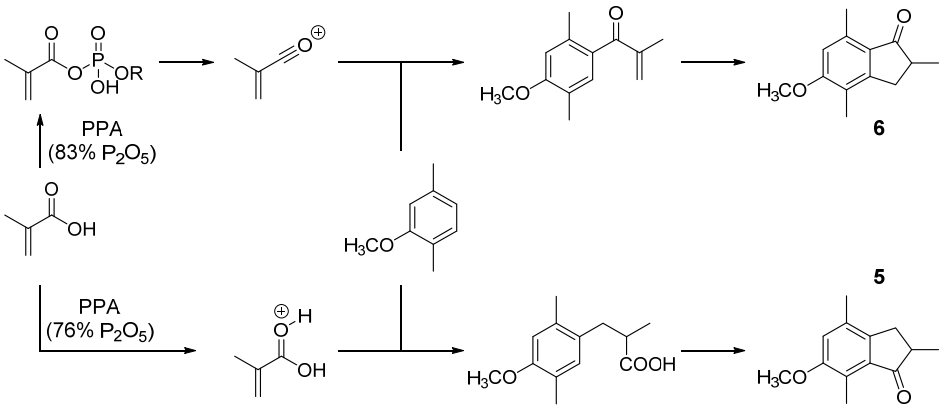
Synthesis of racemic indanones

Indanones **5** and **6** were synthesized from 2,5-dimethyl anisole and methacrylic acid using polyphosphoric acid (PPA) (Scheme 4). PPA is a mixture of oligomers of phosphoric acids with the general formula depicted in scheme 4a. The overall composition of PPA is normally expressed in terms of its theoretical P_2O_5 and H_2O content.[9] It was found that the P_2O_5 content, had great effect on the regioselectivity of the reaction. Using PPA with a P_2O_5 content of 76%, indanone **5** was obtained predominantly, while the use of PPA with 83% P_2O_5 gave mostly indanone **6** (Scheme 4). To the best of the author's knowledge the effect of the PPA composition on the regioselectivity of these type of reactions was not described before. For that reason, a short investigation was conducted into its origin.



Scheme 4: (a) General structure of PPA. (b) Synthesis of indanone **5** and **6**.

First of all, the difference in composition of PPA was apparent in the ^{31}P NMR spectrum. While PPA (76% P_2O_5) consists mostly of H_3PO_4 and some diphosphoric acid, PPA (83% P_2O_5) has a larger fraction of triphosphoric acid and larger oligomers. Analysis of a mixture consisting of 5 wt% methacrylic acid in PPA (83% P_2O_5) at 80 °C indicated the formation of several species, which were identified as phosphoric anhydrides of methacrylic acid. When PPA (76% P_2O_5) was used, no mixed anhydride was observed. These results are also consistent with a literature report on the ratio of benzoic acid and its phosphoric anhydride in PPA of varying P_2O_5 content.[11] Based on these results, the following mechanism is proposed (Scheme 5).



Scheme 5: Proposed mechanism for the switch in regioselectivity.

With PPA (83% P_2O_5), the mixed anhydride of methacrylic acid is formed, which generates the corresponding acylium ion. The anisole performs a nucleophilic attack on this acylium ion to give the intermediate enone. After Nazarov cyclization, indanone **6** is obtained. In the case of PPA (76% P_2O_5), it is proposed that the anisole will react through a competing pathway. The arene adds to the unsaturated carboxylic acid in a 1,4-fashion to afford the carboxylic acid. Subsequent Friedel-Crafts acylation will give indanone **5**. The intermediates in these reactions were never observed, also when the reaction did not reach full conversion, indicating that the intramolecular reaction is faster than the intermolecular reaction, for both reaction pathways.

To examine the generality of the switch in regioselectivity depending on the P_2O_5 content of PPA, several other substrates were tested (Table 1). In all cases, it was found that the composition of PPA has an effect on the regioselectivity, although in some cases more pronounced than in others. The general trend is that PPA with a low P_2O_5 content promotes the formation of the indanone isomer having the electron-donating group meta to the carbonyl functionality, whereas PPA with a high P_2O_5 content favors the formation of the indanone with its electron-donating group ortho or para to the carbonyl functionality. Substitution at either the α or β position of the unsaturated carboxylic acid disfavors formation of product I. The use of electron-poor benzene derivatives resulted in very low yields and was not investigated further.

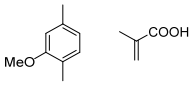
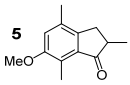
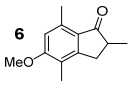
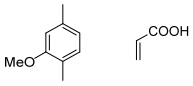
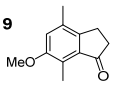
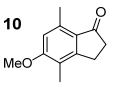
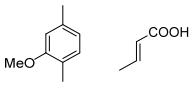
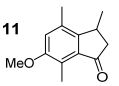
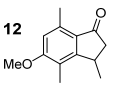
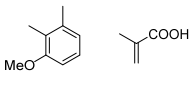
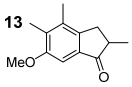
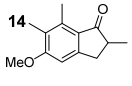
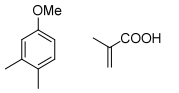
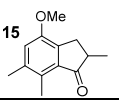
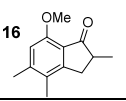
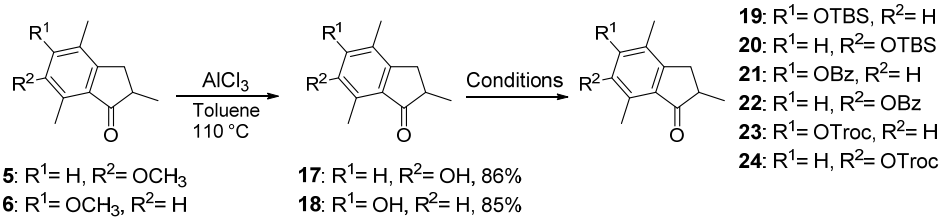
Entry	Reactants	Conditions[a]	Products I	Product II	Ratio (I:II)[b]	Yield (%)
1		**A**			>95:5	64
2		**B**			<5:95	61
3		**A**			>95:5	63
4		**B**			60:40	58
5		**A**			25:75	81
6		**B**			<5:95	88
7		**A**			50:50	82
8		**B**			<5:95	78
9		**A**			85:15	52
10		**B**			15:85	51

Table 1: [a]Condition A: 100 °C, PPA (76% P_2O_5); Condition B: 100 °C, PPA (83% P_2O_5). [b]The regioisomer ratio was determined by analysis of the crude product with ^{1}H NMR spectroscopy.

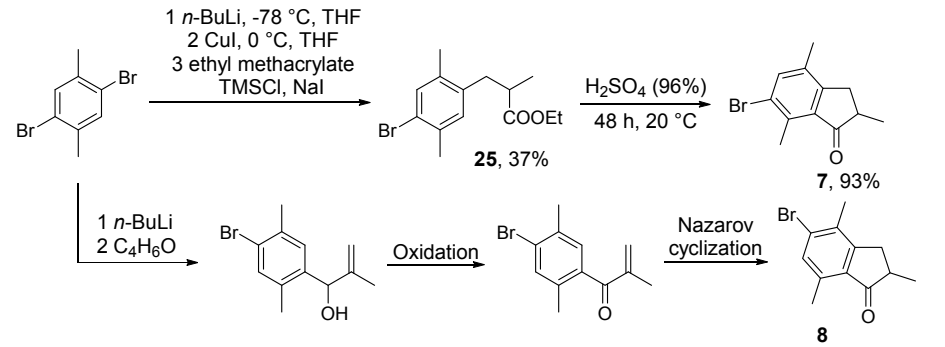
From indanones **5** and **6**, other functionalized indanones could be prepared in a straightforward way. The demethylation proceeded smoothly with $AlCl_3$ at 100 °C in

toluene. At this point various oxygen protecting groups were installed using standard conditions (Scheme 6), in order to investigate the effect of this group on the subsequent enantioselective protonation.



Scheme 6: Synthesis of indanones **5**, **6** and **17**-**24**.

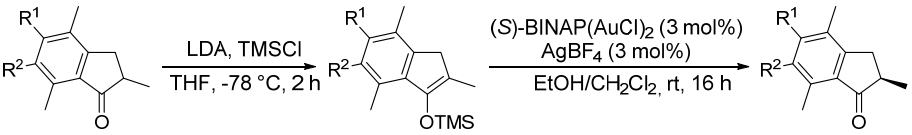
The other precursors, indanone **7** and **8** were prepared from 1,4-dibromo-2,5-dimethyl benzene (Scheme 7). Lithiation with *n*-BuLi, followed by transmetalation with CuI, afforded the cuprate which added to ethyl methacrylate catalyzed by in situ generated TMSI. Cyclization of ethyl ester **25** using H_2SO_4 (96%) afforded compound **7** in two steps with an of overall yield of 34% (based on dibromoxylene). The other regioisomer indanone **8** was prepared by Anouk Lubbe. Lithiation of 1,4-dibromo-2,5-dimethyl benzene with *n*-BuLi, followed by the addition methacryl aldehyde gave the allylic alcohol. Subsequent oxidation and Nazarov cyclization afforded indanone **8**.



Scheme 7: Synthesis of indanone **7** and **8**.

Enantioselective protonation of silyl enol ethers.

With the desired indanones in hand, the silyl enol ether formation and subsequent enantioselective protonation was investigated (Table 2). It was found that the electronic nature of the substituent R^1 and R^2 of the indanone has a large influence on the enantioselectivity of this reaction. The asymmetric protonation of the silyl enol ethers of indanones with bromo substituents proceeded with high selectivity, 97% enantiomer excess (ee) (entry 2) and 94% ee (entry 3), giving a significantly higher enrichment than observed for unsubstituted indanone **26**, which gives 81% ee (entry 1). In the case of



Entry	R^1	R^2	Product	Yield (%)[a]	ee (%)[b]
1	H	H	**26**	85	81
2	H	Br	**7**	86	97
3	Br	H	**8**	88	94
4	H	OTBS	**20**	82	78
5	OTBS	H	**19**	81	7
6	OMe	H	**6**	84	4
7	OBz	H	**21**	86	87
8	H	OBz	**22**	86	98
9	OTroc	H	**23**	27	97
10	H	OTroc	**24**	27	98

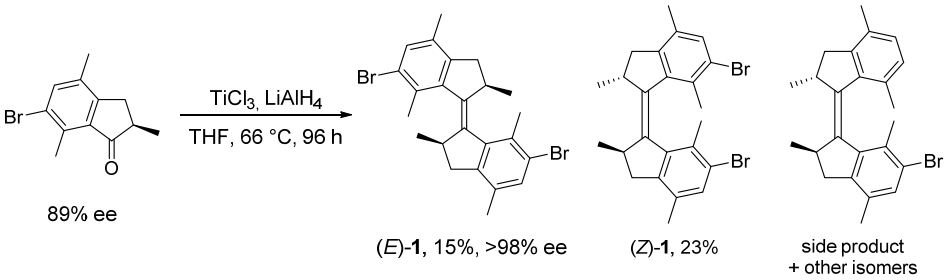
Table 2: [a]Isolated yield over two steps. [b]Determined by chiral HPLC or SFC; The absolute configuration of compound **7** was determined by comparison with literature data.[1a] The configuration of the other compounds were determined by comparison of the optical rotation.

indanones with siloxy- and methoxy-substituents at the R^2 and especially the R^1 position (entries 4−6) the selectivity was considerably lower (4−78% ee), probably due to a faster uncatalyzed background reaction of the silyl enol ether during the reaction. By changing to a more electron-withdrawing protective group of the phenolic group, like benzoate (entries 7 and 8) or carbonate (entries 9 and 10), high stereoselectivity (up to 98% ee) could be regained. However, the use of the 2,2,2-trichloro-ethoxycarbonyl (Troc) protective group (entries 9 and 10) resulted in low yields, due to the incompatibility of this moiety with LDA. The benzoate indanones (entires 7 and 8) were obtained in high yield but this protecting group could not be removed without racemizing the stereocenter. The indanones **19** and **20** were obtained in high optical purity by the deprotection of the Troc group of **23** and **24** using Zn and acetic acid, followed by the reprotection using TBSCl and imidazole.

Synthesis of first generation molecular motors

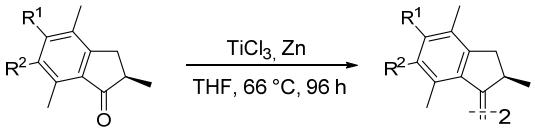
With the enantioenriched ketones in hand, the next step was the formation of the sterically hindered double bond via the McMurry reaction. Using the condition of Harada et al. ($TiCl_3/LiAlH_4$), the desired product **1** was obtained in 38% yield with an *E*/*Z* ratio of 40:60. More surprisingly, the product was obtained with an enantiomeric

excess of >98%, starting from 89% ee for ketone **7**. A rationalization for this observation is given further on. Unfortunately, alkene **1** was obtained as a mixture with dehalogenated byproducts, which were inseparable from the desired product. It has been reported in the literature that the reaction of $TiCl_3$ with $LiAlH_4$ results in the formation of a reactive titanium(II) hydride species.[12] It is well possible that such a species is able to dehalogenate either the starting material or the product.



Scheme 8: McMurry coupling using $TiCl_3$ and $LiAlH_4$.

In an attempt to circumvent the formation of dehalogenated side products, the combination of $TiCl_3$ and zinc was tried (Table 3).[13] Fortunately, with these conditions no dehalogenation occurred and both bromo and TBS functionalized motors could be obtained in high yields and ee's. The Troc and the benzoate protecting group on the other hand were not compatible with the conditions of the McMurry reaction.



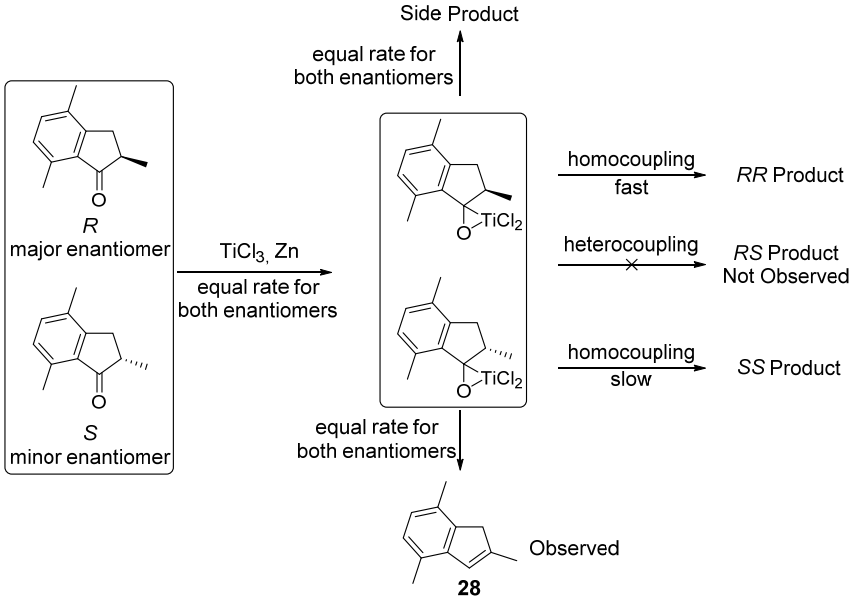
Entry	R^1	R^2	ee ketone (%)	Product	*E*/*Z* ratio[a]	Yield (%)	ee (%)[b]
1	H	Br	97	**1**	50:50	85	99
2	H	Br	94	**1**	45:55	86	97
3	H	Br	89	**1**	50:50	88	93
4	Br	H	94	**2**	40:60	82	98
5	H	H	81	**27**	25:75	81	91
6	H	OTBS	97	**3**	50:50	84	99
7	OTBS	H	96	**4**	44:56	86	97

Table 3: [a]Determined by ^{1}H-NMR spectroscopy, [b]Determined by chiral HPLC or SFC.

Also with Zn as reductant, a small increase of optical purity was observed, although less pronounced compared to the conditions with $LiAlH_4$ as reductant. The absence of

racemization in the McMurry reaction using $TiCl_3$/Zn is remarkable considering that the use of $TiCl_4$/Zn has been reported to result in loss of optical purity.[7] The standard procedure for the McMurry reaction (using $TiCl_4$/Zn) includes the initial reduction of $TiCl_4$ to $TiCl_3$ with Zn as first step, prior to the addition of the ketone. Thus both procedures essentially involve Ti(III) as reagent. Why racemization still occurred with the $TiCl_4$/Zn protocol can be ascribed to an incomplete initial reduction step. Some $TiCl_4$ remains which can, due to its Lewis acidic nature, racemize the substrate.

Another interesting aspect of the McMurry reactions described here is the enhancement of ee, which has not been reported before. It should be noted that the McMurry reaction in all the syntheses of first generation molecular motors is highly diastereoselective. Only the homocoupling products i.e. *RR* and *SS* are obtained. The formation of the *RS* stereoisomer has never been observed. Based on this high stereoselectivity, the following mechanism is proposed. The treatment of a ketone with $TiCl_3$/Zn results in the irreversible formation of a low-valent titanium(II) species (Scheme 9).[12] When this reaction is performed on enantioenriched ketone, the concentration of the titanium(II) complex of e.g. the *R* isomer is higher than for the *S* complex, which will result in a different reaction rate for both dimerization reactions. Due to the longer reaction time required for homocoupling of the minor enantiomer, this isomer is more prone to side reactions such as the one leading to side product **28**, which was obtained in all McMurry reactions using Zn and $TiCl_3$. The overall result of these effects is that a relative larger amount of the minor enantiomer decomposes, with the consequence of an increased ee of the major product.



Scheme 9: Proposed mechanism for the increase of ee caused by the McMurry reaction.

In the case of a strong reductant such as $LiAlH_4$, the increase in ee was larger than when the milder reductant Zn was used (89% ee → >98% versus 89% ee → 94% ee). It is hypothesized that under the harsher reaction conditions, the side reactions are faster and the effect of the concentration-dependency of the dimerization are therefore more pronounced.

2.3 Conclusion

In conclusion, an asymmetric synthesis of functionalized first generation molecular motors has been developed. The catalytic enantioselective protonation of silyl enol ethers by an in situ generated cationic Au(I)BINAP complex followed by a McMurry coupling with an ee amplification step gives access to the enantiomeric enriched first generation molecular motors. Especially the bromo substituted motors **1** and **2** can be obtained in high yield and enantioselectivity. This method however is not practical for the synthesis of oxygen functionalized motors, as it was found that the indanone precursors were difficult to obtain in high optical purity. The developed method have proven very valuable in the asymmetric synthesis of various molecular motors based on the first generation xylene motor.[1b,1c,3c,4c]

2.4 Acknowledgements

Thomas Neubauer is gratefully acknowledged for the optimization of the enantioselective protonation and McMurry reaction. Anouk Lubbe is acknowledged for the synthesis of indanone **8**.

2.5 Experimental Section

General Remarks

^1H NMR and ^{13}C NMR spectra were recorded on a Varian Unity Plus Varian-500 (500 and 125 MHz, respectively), Varian AMX400 (400 and 100 MHz, respectively) or a Varian VXR200-NMR spectrometer (200 MHz and 50 MHz, respectively) with $CDCl_3$ or DMSO as solvent. Chemical shifts were determined relative to the residual solvent peaks ($CHCl_3$, δ = 7.26 ppm for ^1H NMR, δ = 77.0 ppm for ^{13}C NMR; DMSO, δ = 2.50 ppm for ^1H NMR, δ = 39.5 ppm for ^{13}C NMR). The following abbreviations are used to indicate signal multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Enantiomeric excesses were determined by chiral HPLC using a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector or by supercritical fluid chromatography (SFC), performed on a Thar Technologies, Inc. (Waters) Investigator II system. Optical rotations were measured on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL) at 20 °C. Thin-layer chromatography (TLC) was performed on Merck TLC Silica gel 60

Kieselguhr F254. Flash chromatography was performed on silica gel Merck Type 9385 230-400 mesh or on a Reveleris X2 Flash Chromatography system. Mass spectra were recorded on a AEI-MS-902 mass spectrometer (EI+) or a LTQ Orbitrap XL (ESI+). All reagents were obtained from commercial sources and used as received without further purification. Polyphosphoric acid (105% H_3PO_4 basis (= 76% P_2O_5) and 115% H_3PO_4 basis (= 83% P_2O_5)) was purchased from Sigma Aldrich. Solvents for extraction and chromatography were technical grade. All solvents used in reactions were freshly distilled from appropriate drying agents before use or obtained from a MBraun solvent purification system. All other reagents were used without further purification. All reactions were performed under anhydrous conditions in a N_2 atmosphere, unless stated otherwise.

General Procedure A

This reaction was performed under ambient conditions. A mechanically stirred solution of anisole (7.35 mmol, 1.0 eq) and acid (14.7 mmol, 2.0 eq) in ~ 20 g PPA (76% P_2O_5) was heated at 100 °C for 4 h. The reaction mixture was quenched with ice and extracted with Et_2O (3 x 150 mL) The organic layer was washed with a saturated solution of $NaHCO_3$ (aq.) (200 mL) and a 1 M solution of NaOH (aq.) (200 mL) and dried over Na_2SO_4. The solvent was evaporated and the crude product purified by column chromatography (SiO_2, pentane/EtOAc).

General Procedure B

This reaction was performed under ambient conditions. A mechanically stirred solution of anisole (7.35 mmol, 1.0 eq) and acid (14.7 mmol, 2.0 eq) in ~ 20 g PPA (83% P_2O_5) was heated at 100 °C for 4 h. The reaction mixture was quenched with ice and extracted with Et_2O (3 x 150 mL) The organic layer was washed with a saturated solution of $NaHCO_3$ (aq.) (200 mL) and an 1 M solution of NaOH (aq.) (200 mL) and dried over Na_2SO_4. The solvent was evaporated and the crude product purified by column chromatography (SiO_2, pentane/EtOAc).

6-methoxy-2,4,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**5**)

Following general procedure A with 2,5-dimethylanisole and methacrylic acid, a mixture of **5** and **6** was obtained in a ratio of >95:5 in 64% yield. **5** was isolated as white crystals. M.p. 81-82 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (s, 1H), 3.81 (s, 3H), 3.12 (dd, J = 16.6, 8.0 Hz, 1H), 2.71 – 2.52 (m, 1H), 2.48 (s, 3H), 2.43 (dd, J = 16.7, 4.1 Hz, 1H), 2.27 (s, 3H), 1.27 (d, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 210.8, 156.8, 144.2, 134.0, 132.6, 123.8, 117.6, 56.1, 42.7, 32.3, 17.7, 16.4, 9.5; HRMS (ESI+) calcd for $C_{13}H_{17}O_2$ $[M+H]^+$ 205.1223, found 205.1224.

5-methoxy-2,4,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**6**)

Following general procedure B with 2,5-dimethylanisole and methacrylic acid, a mixture of **6** and **5** was obtained in a ratio of >95:5 in 61% yield. **6** was isolated as white crystals. M.p. 76-78 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 1H), 3.87 (s, 3H), 3.18 (dd, *J* = 17.0, 8.0 Hz, 1H), 2.67 – 2.53 (m, 4H), 2.48 (dd, *J* = 17.0, 4.0 Hz, 1H), 2.09 (s, 3H), 1.26 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 208.9, 161.5, 154.2, 137.9, 126.3, 119.8, 111.4, 55.5, 42.2, 33.3, 18.2, 16.5, 10.4; HRMS (ESI+) calcd for $C_{13}H_{17}O_2$ $[M+H]^+$ 205.1223, found 205.1224.

6-methoxy-4,7-dimethyl-2,3-dihydro-1*H*-inden-1-one (**9**)

Following general procedure A with 2,5-dimethylanisole and acrylic acid, a mixture of **9** and **10** was obtained in a ratio of >95:5 in 63% yield. **9** was isolated as white crystals. M.p. 165-166 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (s, 1H), 3.82 (s, 3H), 2.84-2.76 (m, 2H), 2.68 – 2.56 (m, 2H), 2.47 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.5, 156.7, 146.1, 134.7, 132.8, 123.7, 117.6, 56.2, 37.3, 23.1, 17.7, 9.5; HRMS (ESI+) calcd for $C_{12}H_{15}O_2$ $[M+H]^+$ 191.1067, found 191.1058.

5-methoxy-4,7-dimethyl-2,3-dihydro-1*H*-inden-1-one (**10**)

Following general procedure B with 2,5-dimethylanisole and acrylic acid, a mixture of **10** and **9** was obtained in a ratio of 40:60 in 58% yield. **10** was isolated as white crystals. M.p. 144-145 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.61 (s, 1H), 3.89 (s, 3H), 3.23 – 2.75 (m, 2H), 2.68 – 2.54 (m, 5H), 2.13 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 206.9, 161.6, 156.3, 138.0, 127.4, 120.2, 111.5, 55.8, 37.1, 24.3, 18.5, 10.6; HRMS (ESI+) calcd for $C_{12}H_{15}O_2$ $[M+H]^+$ 191.1067, found 191.1067.

6-methoxy-3,4,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**11**)

Following general procedure A with 2,5-dimethylanisole and crotonic acid, a mixture of **11** and **12** was obtained in a ratio of 25:75 in 81% yield. **11** was isolated as white crystals. M.p. 97-98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.89 (s, 1H), 3.84 (s, 3H), 3.40 – 3.34 (m, 1H), 2.91 (dd, *J* = 18.6, 7.7 Hz, 1H), 2.49 (s, 3H), 2.38 (s, 3H), 2.30 (d, *J* = 18.6 Hz, 1H), 1.28 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 208.3, 156.9, 150.6, 134.2, 132.6, 124.0, 118.3, 56.3, 47.3, 30.6, 21.8, 18.1, 9.7; HRMS (ESI+) calcd for $C_{13}H_{17}O_2$ $[M+H]^+$ 205.1223, found 205.1223.

5-methoxy-3,4,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**12**)

Following general procedure B with 2,5-dimethylanisole and crotonic acid, a mixture of **12** and **11** was obtained in a ratio of >95:5 in 88% yield. **12** was isolated as white

crystals. M.p. 71-72 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (s, 1H), 3.89 (s, 3H), 3.47-3.39 (m, 1H), 2.89 (dd, *J* = 18.4, 7.8 Hz, 1H), 2.61 (s, 3H), 2.27 (dd, *J* = 18.4, 1.4 Hz, 1H), 2.18 (s, 3H), 1.27 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 206.4, 162.1, 160.6, 138.1, 126.4, 120.1, 111.6, 55.8, 46.8, 31.5, 21.9, 18.6, 10.9; HRMS (ESI+) calcd for $C_{13}H_{17}O_2$ $[M+H]^+$ 205.1223, found 205.1223.

6-methoxy-2,4,5-trimethyl-2,3-dihydro-1*H*-inden-1-one (**13**)

Following general procedure A with 2,3-dimethylanisole and methacrylic acid, a mixture of **13** and **14** was obtained in a ratio of 50:50 in 82% yield. **13** was isolated as white crystals. M.p. 62-65 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.68 (s, 1H), 3.87 (s, 3H), 3.23 (dd, *J* = 16.5, 7.6 Hz, 1H), 2.79 – 2.50 (m, 5H), 2.11 (s, 3H), 1.26 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.0, 162.5, 154.4, 138.5, 126.6, 125.3, 104.3, 55.5, 42.4, 34.4, 16.7, 13.8, 10.9; HRMS (ESI+) calcd for $C_{13}H_{17}O_2$ $[M+H]^+$ 205.1223, found 205.1223.

5-methoxy-2,6,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**14**)

Following general procedure B with 2,3-dimethylanisole and methacrylic acid, a mixture of **14** to **13** was obtained in a ratio of >95:5 in 78% yield. **14** was isolated as white crystals. M.p. 65-67 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.69 (s, 1H), 3.88 (s, 3H), 3.25 (dd, *J* = 16.7, 7.6 Hz, 1H), 2.75 – 2.46 (m, 5H), 2.13 (s, 3H), 1.27 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 209.1, 162.6, 154.4, 138.6, 126.7, 125.4, 104.3, 55.6, 42.5, 34.4, 16.8, 13.8, 10.9; HRMS (ESI+) calcd for $C_{13}H_{17}O_2$ $[M+H]^+$ 205.1223, found 205.1223.

4-methoxy-2,6,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**15**)

Following general procedure A with 3,4-dimethylanisole and methacrylic acid , a mixture of **15** to **16** was obtained in a ratio of 85:15 in 52% yield. **15** was isolated as white crystals. M.p. 90-91 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (s, 1H), 3.85 (s, 3H), 3.19 (dd, *J* = 17.3, 7.9 Hz, 1H), 2.65 – 2.57 (m, 1H), 2.53 – 2.42 (m, 4H), 2.29 (s, 3H), 1.27 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 210.7, 154.0, 140.2, 137.4, 134.6, 128.1, 116.7, 55.3, 42.3, 30.3, 19.4, 16.5, 12.6; HRMS (ESI+) calcd for $C_{13}H_{17}O_2$ $[M+H]^+$ 205.1223, found 205.1222.

7-methoxy-2,4,5-trimethyl-2,3-dihydro-1*H*-inden-1-one (**16**)

Following general procedure B with 3,4-dimethylanisole and methacrylic acid, a mixture of **16** to **15** was obtained in a ratio of 85:15 in 51% yield. **16** was isolated as white crystals. M.p. 85-86 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.58 (s, 1H), 3.87 (s, 3H), 3.18 (dd, *J* = 17.1, 7.9 Hz, 1H), 2.74 – 2.52 (m, 1H), 2.48 (dd, *J* = 17.1 Hz, 3.5, 1H),

2.30 (s, 3H), 2.10 (s, 3H), 1.24 (d, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 207.1, 155.7, 154.4, 145.6, 125.1, 122.1, 110.8, 55.5, 42.2, 33.9, 20.7, 16.9, 13.5; HRMS (ESI+) calcd for $C_{13}H_{17}O_2$ $[M+H]^+$ 205.1223, found 205.1223.

Ethyl 3-(4-bromo-2,5-dimethylphenyl)-2-methylpropanoate (**25**)

To a solution of 1,4-dibromo-2,5-dimethylbenzene (10.0 g, 37.9 mmol) in THF (200 mL) at −78 °C was added a solution of *n*-BuLi (24.1 mL, 38.6 mmol, 1.6 M in hexane). After addition the reaction mixture was stirred for 30 min and then added via cannula to a suspension of copper(I)-iodide (3.60 g, 18.9 mmol) and sodium iodide (11.4 g, 75.8 mmol) in THF (30 mL). The resulting mixture was stirred at 0 °C for 30 min and cooled to −78 °C. Trimethylsilyl chloride (12.3 g, 14 mL, 114 mmol) was added and stirring was continued for 20 min. Ethyl methacrylate (13.0 g, 114 mmol) was added at −78 °C after which the reaction mixture was heated to 0 °C and stirred for 48 h. A saturated solution of NH_4Cl (aq.) (100 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (2 x 200 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 19:1) to afford **25** as a slight yellow oil (4.20 g, 14.0 mmol, 37% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (s, 1H), 6.95 (s, 1H), 4.09 (q, J = 7.1 Hz, 2H), 2.93 (dd, J = 13.5, 6.9 Hz, 1H), 2.71 – 2.61 (m, 1H), 2.57 (dd, J = 13.5, 7.7 Hz, 1H), 2.31 (s, 3H), 2.25 (s, 3H), 1.18 (m, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 176.0, 136.9, 135.6, 134.8, 133.6, 132.0, 122.3, 60.3, 40.1, 36.4, 22.2, 18.6, 16.9, 14.1; HRMS (ESI+) calcd. for $C_{14}H_{20}BrO_2$ $[M+H]^+$ 209.0641, found: 209.0640.

6-bromo-2,4,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**7**)

H_2SO_4 (10 mL, 96%) was added to the ester **25** (1.00 g, 3.30 mmol) and the mixture was stirred for 36 h at room temperature. The reaction mixture is poured on ice and extracted with Et_2O (2 x 20 mL). The organic layer is washed with a saturated solution of $NaHCO_3$ (aq.) (50 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 9:1) to afford **7** as an off-white solid (0.79 g, 3.10 mmol, 93% yield). M.p. 79-81 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54 (s, 1H), 3.17 (dd, J = 17.2, 8.0 Hz, 1H), 2.82 – 2.54 (m, 4H), 2.47 (dd, J = 17.3, 4.0 Hz, 1H), 2.28 (s, 3H), 1.30 (d, J = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.5, 152.3, 137.8, 135.7, 134.6, 134.3, 124.9, 42.3, 32.7, 17.2, 16.5, 16.5; HRMS (ESI+) calcd. for $C_{12}H_{14}BrO$ $[M+H]^+$ 253.0225, found: 253.0223.

6-hydroxy-2,4,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**17**)

To a solution of **5** (1.50 g, 7.89 mmol) in toluene (30 mL), $AlCl_3$ (3.00 g, 22.6 mmol) was added. The reaction mixture was stirred at 100 °C for 3 h and then cooled to 0 °C.

H_2O (50 mL) was carefully added and the aqueous layer was extracted with EtOAc (4 x 50 mL) The combined organic layers were washed with a saturated $NaHCO_3$ (aq.) (50 mL) solution, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 5:1) to afford **17** as white crystals (1.23 g, 6.79 mmol, 86% yield). M.p. 150-151 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1H), 4.94 (s, 1H), 3.15 (dd, *J* = 16.7, 7.9 Hz, 1H), 2.86 – 2.57 (m, 1H), 2.52 (s, 3H), 2.45 (dd, *J* = 16.8, 3.9 Hz, 1H), 2.25 (s, 3H), 1.29 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 211.7, 153.3, 145.6, 134.2, 133.2, 122.5, 120.3, 42.8, 32.5, 17.5, 16.6, 9.4; HRMS (ESI+) calcd. for $C_{12}H_{15}O_2$ $[M+H]^+$ 191.1067, found: 191.1068; Anal. calcd. for $C_{12}H_{14}O_2$: C 75.76, H 7.42. Found: C 75.75, H 7.44.

5-hydroxy-2,4,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**18**)

$AlCl_3$ (2.40 g, 18 mmol) was added to a solution of **6** (1.20 g, 5.90 mmol) in toluene (20 mL). The reaction mixture was heated to 100 °C for 3 h and then cooled to 0 °C. H_2O (50 mL) was carefully added and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers were, dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 5:1) to afford **18** as a slight brown solid (0.95 g, 5.00 mmol, 85% yield). M.p. 194-195 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 6.57 (s, 1H), 5.64 (br, 1H), 3.22 (dd, *J* = 17.0, 7.9 Hz, 1H), 2.82 – 2.31 (m, 5H), 2.16 (s, 3H), 1.29 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 208.1, 160.8, 155.9, 136.9, 125.4, 118.1, 116.7, 42.1, 33.4, 18.1, 17.0, 10.9; HRMS (ESI+) calcd. for $C_{12}H_{15}O_2$ $[M+H]^+$ 191.1067, found: 191.1059.

6-((*tert*-butyldimethylsilyl)oxy)-2,4,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**20**)

To a solution of **17** (1.00 g, 3.29 mmol) in CH_2Cl_2 (10 mL) was added 4-dimethylaminopyridine (482 mg, 3.95 mmol) and *tert*-butyldimethylsilyl chloride (543 mg, 3.62 mmol). The reaction mixture was stirred for 16 h. A saturated NH_4Cl (aq.) (50 mL) solution was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), the organic solutions was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 99:1) to afford **20** as white solid (950 mg, 3.13 mmol, 95% yield). M.p. 87-89 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.83 (s, 1H), 3.15 (dd, J = 16.7, 7.9 Hz, 1H), 2.65 (pd, *J* = 7.5, 4.1 Hz, 1H), 2.50 – 2.40 (m, 4H), 2.24 (s, 3H), 1.29 (d, *J* = 7.4 Hz, 3H), 1.02 (s, 9H), 0.19 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.9, 153.0, 145.8, 134.6, 132.5, 125.9, 125.9, 42.6, 32.5, 25.8, 18.3, 17.6, 16.5, 10.7, -4.2; HRMS (ESI+) calcd. for $C_{18}H_{29}O_2Si$ $[M+H]^+$ 305.1913, found: 305.1913.

5-((*tert*-butyldimethylsilyl)oxy)-2,4,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**19**)

To a solution of **18** (1.00 g, 5.30 mmol) in CH_2Cl_2 (10 mL) was added 4-dimethylaminopyridine (482 mg, 3.95 mmol) and *tert*-butyldimethylsilyl chloride (543 mg, 3.62 mmol). The reaction mixture was stirred for 16 h. A saturated NH_4Cl (aq.) (50 mL) solution was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 99:1) to afford **19** as clear oil (1.53 g, 5.04 mmol, 94% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (s, 1H), 3.20 (dd, *J* = 17.1, 8.0 Hz, 1H), 2.68 – 2.60 (m, 1H), 2.55 (s, 3H), 2.50 (dd, *J* = 17.1, 3.9 Hz, 1H), 2.11 (s, 3H), 1.28 (d, *J* = 7.4 Hz, 3H), 1.02 (s, 9H), 0.26 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 209.3, 158.5, 155.5, 137.6, 127.3, 122.6, 120.1, 42.4, 33.8, 25.7, 18.3, 18.2, 16.7, 11.3, -4.1; HRMS (ESI+) calcd. for $C_{18}H_{29}O_2Si$ $[M+H]^+$ 305.1913, found: 305.1923.

2,4,7-trimethyl-1-oxo-2,3-dihydro-1*H*-inden-5-yl benzoate (**21**)

To a solution of **18** (1.17 g, 6.16 mmol) in CH_2Cl_2 (20 mL) was added pyridine (758 mg, 9.48 mmol) and benzoyl chloride (751 mg, 6.47 mmol) at 0 °C. The reaction mixture was stirred for 16 h at room temperature. A saturated NH_4Cl (aq.) (50 mL) solution was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 20:1) to afford **21** as white solid (1.67 g, 5.67 mmol, 92% yield). M.p. 84-85 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 7.6 Hz, 2H), 7.66 (t, *J* = 7.4 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 6.94 (s, 1H), 3.28 (dd, *J* = 17.2, 7.9 Hz, 1H), 2.76 – 2.67 (m, 1H), 2.63 (s, 3H), 2.61 – 2.54 (m, 1H), 2.15 (s, 3H), 1.32 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.6, 164.6, 155.4, 153.4, 137.7, 133.9, 131.7, 130.2, 130.1, 129.0, 128.7, 125.0, 123.4, 42.5, 33.7, 18.9, 16.5, 11.4; HRMS (ESI+) calcd. for $C_{19}H_{19}O_3$ $[M+H]^+$ 295.1329, found: 295.1328.

2,4,7-trimethyl-3-oxo-2,3-dihydro-1*H*-inden-5-yl benzoate (**22**)

To a solution of **17** (1.01 g, 5.30 mmol) in CH_2Cl_2 (20 mL) was added pyridine (652 mg, 8.15 mmol) and benzoyl chloride (645 mg, 5.56 mmol) at 0 °C. The reaction mixture was stirred for 16 h at room temperature. A saturated solution of NH_4Cl (aq) (50 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), the organic phase was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 20:1) to afford **22** as white solid (1.48 g, 5.04 mmol, 95% yield). M.p. 136.0-136.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.24 (d, *J* = 8.6 Hz, 2H), 7.66 (t, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.6 Hz, 2H), 7.17 (s, 1H), 3.23 (dt, *J* = 22.7, 11.3 Hz, 1H), 2.72 (pd, *J* = 7.5, 4.0 Hz, 1H), 2.54 (dd, *J* = 17.1, 4.0 Hz, 1H), 2.49 (s, 3H), 2.32 (s, 3H), 1.32 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.1, 165.1, 150.9, 148.6, 134.7, 133.7, 133.6, 130.2, 129.1,

128.6, 128.4, 127.8, 42.6, 32.9, 17.5, 16.5, 10.5; HRMS (ESI+) calcd. for $C_{19}H_{19}O_3$ $[M+H]^+$ 295.1329, found: 295.1329.

2,2,2-trichloroethyl (2,4,7-trimethyl-1-oxo-2,3-dihydro-1*H*-inden-5-yl) carbonate (**23**)

To a solution of **18** (1.00 g, 5.30 mmol) in CH_2Cl_2 (10 mL) was added triethylamine (758 mg, 7.50 mmol) and 2,2,2-trichlorethoxycarbonyl chloride (1.23 g, 5.83 mmol) at 0 °C. The reaction mixture was stirred for 16 h at room temperature. Saturated NH_4Cl (aq.) (50 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 9:1) to afford **23** as yellow oil (1.79 g, 4.93 mmol, 93% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.90 (s, 1H), 4.88 (s, 2H), 3.25 (dd, *J* = 17.2, 7.9 Hz, 1H), 2.72 – 2.64 (m, 1H), 2.58 (s, 3H), 2.55 (d, *J* = 13.1 Hz, 1H), 2.16 (s, 3H), 1.28 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 209.5, 155.7, 152.8, 152.4, 138.2, 132.4, 124.8, 122.7, 94.4, 77.4, 42.74 33.8, 18.2, 16.6, 11.3; HRMS (ESI+) calcd. for $C_{15}H_{16}Cl_3O_4$ $[M+H]^+$ 365.0187, found: 365.0153.

2,2,2-trichloroethyl (2,4,7-trimethyl-3-oxo-2,3-dihydro-1*H*-inden-5-yl) carbonate (**24**)

To a solution of **17** (1.00 g, 5.30 mmol) in CH_2Cl_2 (10 mL) was added triethylamine (758 mg, 7.50 mmol) and 2,2,2-trichlorethoxycarbonyl chloride (1.23 g, 5.83 mmol) at 0 °C. The reaction mixture was stirred for 16 h at room temperature. A saturated solution of NH_4Cl (aq.) (50 mL) was added and the aqueous phase was extracted with CH_2Cl_2 (3 x 10 mL), the organic solutions was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc 9:1) to afford **24** as white solid (1.81 g, 4.98 mmol, 94% yield). M.p. 109-110 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.13 (s, 1H), 4.87 (s, 2H), 3.20 (dd, *J* = 17.1, 7.8 Hz, 1H), 2.76 – 2.60 (m, 1H), 2.56 – 2.44 (m, 1H), 2.48 (s, 3H), 2.29 (s, 3H), 1.29 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 210.0, 152.9, 151.7, 148.6, 135.0, 134.2, 127.7, 127.6, 94.4, 77.4, 42.9, 33.1, 17.7, 16.6, 10.4; HRMS (ESI+) calcd. for $C_{15}H_{16}Cl_3O_4$ $[M+H]^+$ 365.0187, found: 365.0193.

2,4,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**26**)

Compound **26** was prepared according to literature[14] as a low-melting solid. M.p. 34-35 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.22 (d, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.4 Hz, 1H), 3.22 (dd, *J* = 17.1, 7.9 Hz, 1H), 2.70 – 2.60 (m, 1H), 2.58 (s, 3H), 2.52 (dd, *J* = 17.1, 3.7 Hz, 1H), 2.27 (s, 3H), 1.28 (d, *J* = 7.4 Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$) δ 210.9, 153.2, 136.3, 134.6, 133.6, 132.8, 129.4, 42.2, 33.6, 18.1, 17.6, 16.7; HRMS (ESI+) calcd. for $C_{12}H_{15}O$ $[M+H]^+$ 175.1117, found 175.1117.

General Procedure C

To a solution of racemic ketone (1.00 equiv) in THF (0.1 M) was added lithium diisopropylamide (1.05 equiv) at −78 °C. The reaction mixture was stirred for 2 h at −78 °C. After 2 h, trimethylsilyl chloride (1.20 equiv) was added to the reaction mixture. The reaction mixture was allowed to warm up to room temperature and stirred for an additional 2 h. Subsequently, the reaction mixture was cooled to 0 °C and hydrolyzed with saturated $NaHCO_3$ (aq.), extracted with Et_2O (3 x 25 mL), followed by brine, the organic layer was dried over Na_2SO_4 and concentrated in vacuo. The residue was filtered over a plug of silica and directly submitted to the next step without further purification. A solution of (*S*)-BINAP(AuCl)$_2$ (0.006 M in CH_2Cl_2, 0.03 equiv) and a solution of $AgBF_4$ (0.006 M in EtOH, 0.03 equiv) were added at room temperature to a Schlenk flask. The reaction mixture was stirred for 45 min at room temperature, before cooling down to 0 °C. The catalyst solution was added to the silyl enol ether at 0 °C. The reaction mixture was allowed to warm up to room temperature and stirred overnight. The reaction mixture was hydrolyzed with saturated $NaHCO_3$ (aq.), extracted with Et_2O, the organic layer was dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, pentane/EtOAc) to afford (*R*)-ketone.

(*R*)-2,4,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**26**)

The product was obtained according to General Procedure C as a colorless liquid (393 mg, 2.26 mmol, 85% over two steps) and 81% ee. Enantiomeric excess determined by chiral HPLC analysis, Chiralpak OJ-H (98% *n*-heptane/2% *i*-PrOH), 40 °C, 0.5 mL/min, retention times (min) 12.1 (minor) and 12.6 (major); $[\alpha]_D^{20}$= −39.0° (*c*= 1.1, $CHCl_3$); Spectroscopic data identical with those reported above.

(*R*)-6-bromo-2,4,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**7**)

The product was obtained according to General Procedure C as a white solid (425 mg, 1.67 mmol, 85% over two steps) and 94% ee. Enantiomeric excess determined by chiral HPLC analysis, Chiralpak OJ-H (98% *n*-heptane/2% *i*-PrOH), 40 °C, 0.5 mL/min, retention times (min) 14.0 (minor) and 14.5 (major); Absolute configuration determined by comparison with literature.[1a] $[\alpha]_D^{20}$= −34.2° (*c*= 1.1, $CHCl_3$); M.p. 80-81 °C; Spectroscopic data identical with those reported above.

(*R*)-6-((*tert*-butyldimethylsilyl)oxy)-2,4,7-trimethyl-2,3-dihydro-1*H*-inden-1-one **(20)**

The product was obtained according to General Procedure C as a white solid (462 mg, 1.52 mmol, 81% over two steps) and 78% ee. Enantiomeric excess determined by chiral SFC analysis, Chiralpak IA (100% CO_2), 180 bar, 40 °C, 3.5 mL/min, retention times

(min) 5.1 (minor) and 6.1 (major); M.p. 85-86 °C; Spectroscopic data identical with those reported above.

(*R*)-2,4,7-trimethyl-3-oxo-2,3-dihydro-1*H*-inden-5-yl benzoate (**22**)

The product was obtained according to General Procedure C as a white solid (503 mg, 1.71 mmol, 86% over two steps) and 97% ee. Enantiomeric excess determined by chiral SFC analysis, Chiralpak IC (Gradient: 100% CO_2 → 90% CO_2/10% MeOH in 50 min), 150 bar, 40 °C, 2.0 mL/min retention times (min) 31.0 (major) and 32.9 (minor); $[\alpha]_D^{20}$= −30.5° (*c*= 1.1, $CHCl_3$); M.p. 97-98 °C; Spectroscopic data identical with those reported above.

(*R*)-2,2,2-trichloroethyl (2,4,7-trimethyl-3-oxo-2,3-dihydro-1*H*-inden-5-yl) carbonate (**24**)

The product was obtained according to General Procedure C as a yellow oil (86.7 mg, 0.238 mmol, 15% over two steps, 27% based on recovered racemic ketone after silyl enol formation) and 98% ee. Enantiomeric excess determined by chiral SFC analysis, Chiralpak IA (94% CO_2/6% MeOH), 150 bar, 40 °C, 2.0 mL/min, retention times (min) 7.5 (major) and 8.9 (minor); $[\alpha]_D^{20}$= −29.1° (*c*= 1.1, $CHCl_3$); M.p. 107-108 °C; Spectroscopic data identical with those reported above.

(*R*)-5-((*tert*-butyldimethylsilyl)oxy)-2,4,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**19**)

The product was obtained according to General Procedure C as a colorless liquid (565 mg, 1.86 mmol, 81% over two steps) and 7% ee. Enantiomeric excess determined by chiral SFC analysis, Chiralpak IC (87% CO_2/13% *i*-PrOH), 180 bar, 40 °C, 3.5 mL/min, retention times (min): 3.0 (minor) and 3.5 (major); Spectroscopic data identical with those reported above.

(*R*)-5-methoxy-2,4,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**6**)

The product was obtained according to General Procedure C as a colorless liquid (350 mg, 1.72 mmol, 84% over two steps) and 4% ee. Enantiomeric excess determined by chiral HPLC analysis, Chiralpak OJ-H (98% *n*-heptane/2% *i*-PrOH), 40 °C, 0.5 mL/min, retention times (min) 16.7 (major) and 19.3 (minor); M.p. 76-77 °C; Spectroscopic data identical with those reported above.

(*R*)-2,4,7-trimethyl-1-oxo-2,3-dihydro-1*H*-inden-5-yl benzoate (**21**)

The product was obtained according to General Procedure C as a white solid (559 mg, 1.90 mmol, 86% over two steps) and 86% ee. Enantiomeric excess determined by chiral

SFC analysis, Chiralpak IB (99% CO_2/1% EtOH), 150 bar, 40 °C, 2.0 mL/min, retention times (min) 25.9 (minor) and 27.1 (major); $[\alpha]_D^{20}$= −9.6° (*c*= 1.1, $CHCl_3$); M.p. 102-103 °C; Spectroscopic data identical with those reported above.

(*R*)-2,2,2-trichloroethyl (2,4,7-trimethyl-1-oxo-2,3-dihydro-1*H*-inden-5-yl) carbonate (**23**)

The product was obtained according to General Procedure C as a yellow oil (120 mg, 0.329 mmol, 15% over two steps, 27% based on recovered racemic ketone after silyl enol formation) and 97% ee. Enantiomeric excess determined by chiral SFC analysis, Chiralpak IB (100% CO_2), 130 bar, 40 °C, 3.5 mL/min, retention times (min) 13.1 (minor) and 13.5 (major); $[\alpha]_D^{20}$= −17.7° (*c*= 1.1, $CHCl_3$); Spectroscopic data identical with those reported above.

(*R*)-5-((*tert*-butyldimethylsilyl)oxy)-2,4,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**19**)

To a solution of the **23** (170 mg, 0.466 mmol) in DMF (3 mL) at 0 °C was added a suspension of zinc powder (350 mg, 5.38 mmol) in acetic acid (0.3 mL). The suspension was sonicated for 5 min, followed by 45 min of stirring at 0 °C. The reaction mixture was filtered over celite, diluted with a saturated solution of $NaHCO_3$ (aq.) (20 mL) and extracted with EtOAc (4 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was dissolved in DMF (2 mL) and cooled to 0 °C. To the reaction solution imidazole (63.2 mg, 0.93 mmol) and *tert*-butyldimethylsilyl chloride (90.9 mg, 0.606 mmol) were added. After 1 h at room temperature a solution of NH_4Cl (aq.) (20 mL) was added and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O 9/1) to afford **19** as yellow oil (119 mg, 0.391 mmol, 84% yield over two steps) in 96% ee. Enantiomeric excess determined by chiral SFC analysis, Chiralpak IC (87% CO_2/13% *i*-PrOH), 180 bar, 40 °C, 3.5 mL/min, retention times (min) 3.0 (minor) and 3.5 (major); $[\alpha]_D^{20}$= −12.1° (*c*= 0.95, $CHCl_3$); Spectroscopic data identical with those reported above.

(*R*)-6-((*tert*-butyldimethylsilyl)oxy)-2,4,7-trimethyl-2,3-dihydro-1*H*-inden-1-one (**20**)

To a solution of the **24** (50.0 mg, 0.137 mmol) in DMF (2 mL) at 0 °C was added a suspension of zinc powder (110 mg, 1.69 mmol) in acetic acid (0.2 mL). The suspension was sonicated for 5 min, followed by 45 min of stirring at 0 °C. The reaction mixture was filtered over celite, diluted with a saturated solution of $NaHCO_3$ (aq.) (10 mL) and extracted with EtOAc (4 x 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was dissolved in DMF

(1 mL) and cooled to 0 °C. To the reaction solution imidazole (13.9 mg, 0.206 mmol) and *tert*-butyldimethylsilyl chloride (26.7 mg, 0.178 mmol) were added. After 1 h at room temperature a solution of NH_4Cl (aq.) (10 mL) was added and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O 9/1) to afford **20** as white solid (35.4 mg, 0.116 mmol, 85% yield over two steps) in 97% ee. Enantiomeric excess determined by chiral SFC analysis, Chiralpak IA (100% CO_2), 180 bar, 41 °C, 3.5 mL/min, retention times (min) 5.1 (minor) and 6.1 (major); $[\alpha]_D^{20} = -32.6°$ (*c*= 1.1, $CHCl_3$); M.p. 85-86 °C; Spectroscopic data identical with those reported above.

General Procedure D

Ketone (1.0 equiv), zinc powder (4.2 equiv) and $TiCl_3$ (2.1 equiv) were suspended in THF (0.04 M) and heated at reflux for 96 h. After cooling down to room temperature the reaction mixture was filtered over celite and washed with CH_2Cl_2. The filtrate was washed with a solution of NH_4Cl (aq.), which was reextracted with CH_2Cl_2 (3 x 50 mL) The combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The crude product was purified by column chromatography (SiO_2, pentane/Et_2O) to afford the coupling product as an *E*/*Z*-mixture.

(2*R*,2'*R*)-6,6'-dibromo-2,2',4,4',7,7'-hexamethyl-2,2',3,3'-tetrahydro-1,1'-biindenylidene (*E*/*Z* mixture) (**1**)

Product **1** was obtained according to General Procedure D as a white solid (712 mg, 2.80 mmol, 85% yield) as an *E*/*Z*-mixture of 50:50 and 99% ee (*E* and *Z*). Enantiomeric excess determined by chiral SFC analysis, Chiralpak IA (96% CO_2/4% MeOH), 150 bar, 40 °C, 2.0 mL/min retention times (min) *Z*: 8.2 (minor) and 8.5 (major) *E*: 10.1 (minor) and 10.9 (major); *Z*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 (s, 2H), 3.35 (p, *J* = 6.6 Hz, 2H), 3.04 (dd, *J* = 15.1, 6.3 Hz, 2H), 2.41 (d, *J* = 15.2 Hz, 2H), 2.24 (s, 6H), 1.51 (s, 6H), 1.08 (d, *J* = 6.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3, 141.4, 141.2, 132.6, 132.3, 131.9, 123.5, 41.6, 38.4, 21.3, 20.3, 17.9; *E*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 (s, 2H), 2.83 (p, *J* = 6.3 Hz, 2H), 2.58 (dd, *J* = 14.6, 5.6 Hz, 2H), 2.46 (s, 6H), 2.22 (d, *J* = 10.7 Hz, 2H), 2.17 (s, 6H), 1.10 (d, *J* = 5.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 142.2, 142.1, 133.2, 131.7, 130.8, 123.5, 42.1, 38.8, 23.0, 18.9, 18.1; HRMS (ESI+) calcd. for $C_{24}H_{27}Br_2$ $[M+H]^+$ 475.0454, found: 475.0446.

(2*R*,2'*R*)-2,2',4,4',7,7'-hexamethyl-2,2',3,3'-tetrahydro-1,1'-biindenylidene (*E*/*Z* mixture) (**27**)

Product **27** was obtained according to General Procedure D as a white solid (158 mg, 0.500 mmol, 86% yield) as an *E*/*Z*-mixture of 25:75 and 85% ee (*Z*) respectively 91% ee (*E*). Enantiomeric excess determined by chiral SFC analysis, Chiralpak IB (100% CO_2), 150 bar, 40 °C, 1.0 mL/min retention times (min) *Z*: 10.8 (major) and 11.5 (minor) *E*: 14.4 (major) and 15.2 (minor); *Z*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.92 (d, *J* = 7.6 Hz, 2H), 6.85 (d, *J* = 7.7 Hz, 2H), 3.35 (p, *J* = 6.8 Hz, 2H), 3.09 (dd, *J* = 15.0, 6.4 Hz, 2H), 2.44 (d, *J* = 14.9 Hz, 2H), 2.26 (s, 6H), 1.51 (s, 6H), 1.07 (d, *J* = 6.8 Hz, 6H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 144.2, 140.8, 140.7, 133.2, 130.4, 127.8, 127.8, 41.6, 38.9, 21.6, 20.4, 18.4; *E*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.01 (d, *J* = 7.7 Hz, 2H), 6.96 (d, *J* = 7.6 Hz, 2H), 2.90 (p, *J* = 6.2 Hz, 2H), 2.68 (dd, *J* = 14.5, 6.0 Hz, 2H), 2.45 (s, 6H), 2.24 (d, *J* = 13.9 Hz, 2H), 2.20 (s, 6H), 1.09 (d, *J* = 5.0 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6, 141.4, 140.9, 131.2, 131.1, 128.3, 127.8, 41.9, 39.0, 21.9, 19.4, 18.3; Spectroscopic data are identical with those reported in literature.[5]

(((2*R*,2'*R*)-2,2',4,4',7,7'-hexamethyl-2,2',3,3'-tetrahydro-[1,1'-biindenylidene]-6,6'-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (*E*/*Z* mixture) (**3**)

Product **3** was obtained according to General Procedure D as a white solid (26.1 mg, 0.091 mmol, 92% yield) as an *E*/*Z*-mixture of 60:40. Determination of the enantiomeric excess of deprotected silylether showed 99% ee (*E* and *Z*). Enantiomeric excess determined by chiral SFC analysis, Chiralpak IA (92% CO_2/8% MeOH), 150 bar, 40 °C, 2.0 mL/min, retention times (min) *Z*: 11.0 (minor) and 12.9 (major) *E*: 15.2 (major) and 17.2 (minor); *Z*: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.28 (s, 2H), 3.15 – 3.08 (m, 2H), 2.81 (dd, *J* = 14.4, 6.1 Hz, 2H), 2.16 (d, *J* = 14.4 Hz, 2H), 2.01 (s, 6H), 1.20 (s, 6H), 0.90 – 0.84 (m, 6H), 0.77 (s, 18H), 0.07 (d, 6H); 0.05 (d, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 152.3, 142.7, 141.2, 136.9, 130.7, 124.5, 118.3, 42.2, 38.4, 26.1, 18.9, 18.7, 18.6, 18.4, -3.8, -3.8; *E*: ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) = 6.30 (s, 2H), 2.64 (dt, *J* = 10.2, 5.0 Hz, 2H), 2.41 (dd, *J* = 14.0, 5.3 Hz, 2H), 2.07 (s, 6H), 1.96 - 1.94 (m, 2H), 1.94 (s, 6H), 0.86 (s, 18H), 0.0 (s, 12H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) = 152.8, 142.9, 141.8, 135.0, 131.5, 122.9, 118.2, 42.5, 38.7, 26.1, 20.7, 19.5, 17.3, 15.2, -3.8, -4.0; HRMS (ESI+) calcd. for $C_{36}H_{57}O_2Si_2$ $[M+H]^+$ 577.3892, found: 577.3890.

(((2*R*,2'*R*)-2,2',4,4',7,7'-hexamethyl-2,2',3,3'-tetrahydro-[1,1'-biindenylidene]-5,5'-diyl)bis(oxy))bis(*tert*-butyldimethylsilane) (*E*/*Z* mixture) (**4**)

Product **4** was obtained according to General Procedure D as a white solid (354.6 mg, 0.748 mmol, 89% yield) as an *E/Z*-mixture of 50:50. Determination of the enantiomeric excess of the deprotected silylether showed 97% ee (*Z* only). Enantiomeric excess determined by chiral SFC analysis, Chiralpak IA (90% CO_2/10% MeOH), 230 bar,

40 °C, 3.5 mL/min retention times (min) *Z*: 10.1 (minor) and 11.2 (major); *Z*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (d, *J* = 14.5 Hz, 2H), 3.26 (dq, *J* = 13.1, 6.4 Hz, 2H), 3.01 (dd, *J* = 14.6, 6.3 Hz, 2H), 2.37 (d, *J* = 18.2 Hz, 2H), 2.10 (s, 6H), 1.48 (s, 6H), 1.05 (d, *J* = 6.9 Hz, 6H), 1.01 (s, 18H), 0.21 (s, 6H), 0.18 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.8, 150.3, 138.7, 137.6, 135.4, 125.7, 122.2, 45.8, 43.4, 30.1, 24.9, 22.6, 16.8, 0.2, 0.0. *E*: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.47 (s, 2H), 2.83 (p, *J* = 5.9 Hz, 2H), 2.64 (dd, *J* = 14.5, 5.7 Hz, 2H), 2.35 (s, 6H), 2.18 (d, *J* = 14.5 Hz, 2H), 2.04 (s, 6H), 1.05 - 1.03 (m, 6H), 1.01 (s, 18H), 0.26 (s, 3H), 0.23 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 156.7, 148.7, 144.0, 138.4, 135.4, 126.5, 122.1, 46.3, 43.6, 30.0, 26.4, 22.56, 16.7, 0.2, 0.0; HRMS (ESI+) calcd. for $C_{36}H_{57}O_2Si_2$ $[M+H]^+$ 577.3892, found: 577.3882.

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