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Stereoselective preparation of chiral polyfunctional secondary alkyllithiums and alkylcoppers and their application towards natural product synthesis

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Erklärung

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Eidesstattliche Versicherung

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Varvara Morozova

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The true delight is in the finding out rather than in the knowing.

Isaac Asimov

Parts of this PhD Thesis have been published:

1) **V. Morozova**, K. Moriya, P. Mayer, P. Knochel. Stereoselective Synthesis and Retentive Trapping of α-Chiral Secondary Alkyllithiums Leading to Stereodefined α,β-Dimethyl Carboxylic Esters. *Chem. Eur. J.* **2016**, *22*, 9962.

2) **V. Morozova**, J. Skotnitzki, K. Moriya, K. Karaghiosoff, P. Knochel. Preparation of Optically Enriched Secondary Alkyllithium and Alkylcopper Reagents. Synthesis of (-)-Lardolure and Siphonarienal. *Angew. Chem. Int. Ed.* **2018**, *57,* 5516.

Contents

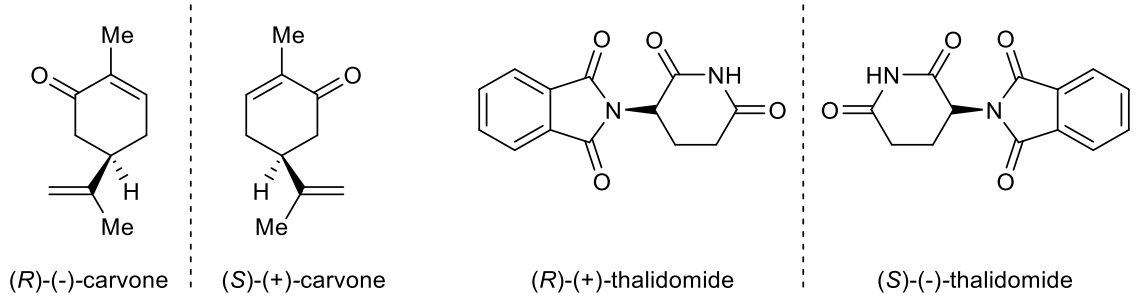
Introduction

Overview

Optical activity

In 1848 French chemist Louis Pasteur separated sodium-ammonium salts of racemic tartaric acid into two different compounds which were absolutely identical according to their chemical and physical properties, apart from their rotation of the plane of polarized light or optical rotations.[1] Based on this observation, it was concluded that these molecules have different three dimensional structures. In 1874, Jacobus Henricus van't Hoff and Joseph Le Bel explained optical activity in terms of the tetrahedral arrangement of the atoms bound to carbon.[2,3]

The molecules are optically active or chiral when they could not match their own mirror image and they are called enantiomers. Enantiomers have exactly the same chemical and physical properties in a symmetrical environment, but different behavior in an unsymmetrical environment, for example, in biological systems. For many biologically active compounds enantiomers behave differently: the one enantiomer has a specific activity while the other enantiomer shows no activity at all or acts completely contrastively. For example, (*R*)-carvone has a smell of spearmint and (*S*)-carvone has a smell of caraway (Scheme 1).[4] Another example is thalidomide – a racemic drug, which was used against nausea and morning sickness of pregnant women. However only the (*R*)-isomer has this biological activity (Scheme 1). Several years after the market entry, it was found that women, who used thalidomide during the pregnancy, gave birth to infants with defects and only 50% of these children survived.[5] Some studies showed, that the (*S*)-isomer of thalidomide is teratogenic and causes infants deformation of limbs. Epimerization of thalidomide *in vivo* limits the use of pure (*R*)-isomer, since (*S*)-isomer is always present as well.[6]



Scheme 1. Structures of carvone and thalidomide.

Thus, the synthesis and isolation of enantiopure compounds is a very important task in organic synthesis. There are two fundamental approaches to access stereodefined molecules: the first and the oldest one is the separation of racemic mixtures. The second one is enantioselective synthesis.[7] Each approach has several advantages and disadvantages and both strategies will be discussed in detail further.

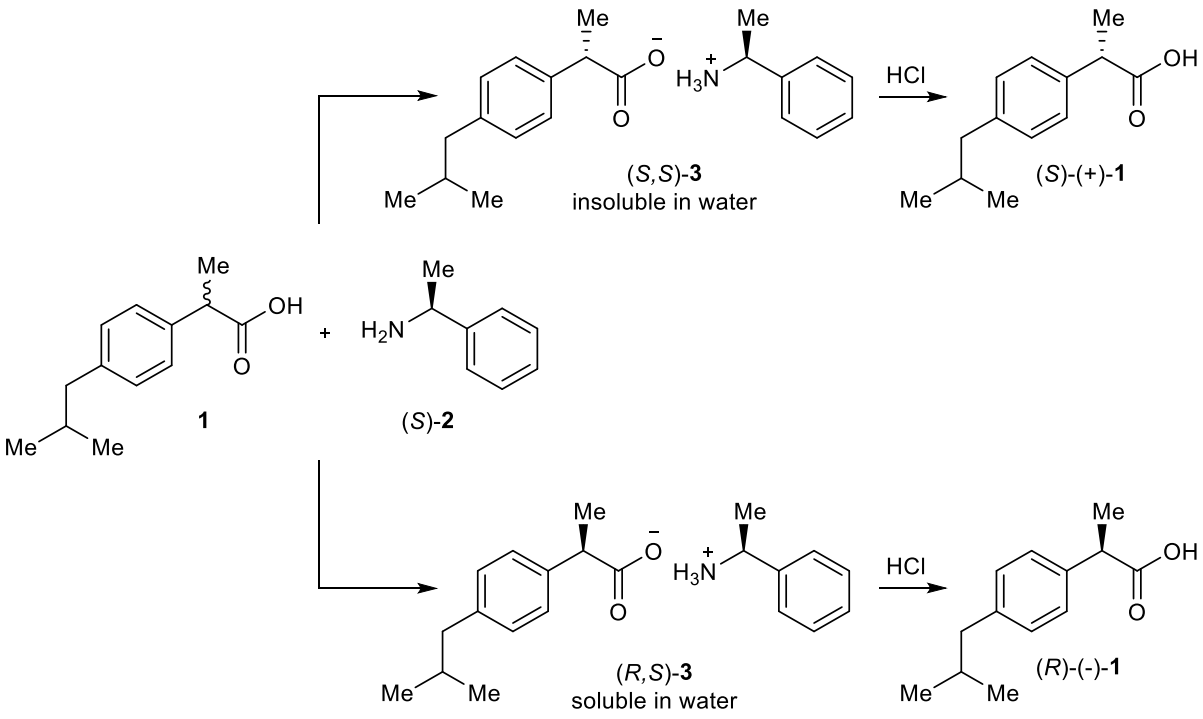
Access to chiral molecules

Separation of racemic mixtures

In a chiral separation the racemate is placed into an unsymmetrical environment and as a result the enantiomers have different behaviour and can be separated. An unsymmetrical environment can be, for example, a chemical transformation, involving a reaction with a chiral agent, or a chiral material, which interacts differently with enantiomers, or a biological system.[7] Here the mostly used chiral resolution methods will be discussed.

Chiral derivatization

If both enantiomers react with an optically active compound with similar rates, the 1:1 mixture of diastereomers is formed. The obtained diastereomers have different physical properties and therefore they can be separated during purification, for example, by recrystallization or column chromatography. This method is called chiral derivatization.[7,8] After the separation, the diastereomers are usually converted back to the original substances and used further as enantiopure compounds. For example, racemic ibuprofen (**1**) reacts with (*S*)-(-)-1-phenylethylamine (*S*)-**2** to produce corresponding mixture of salts (**3**), whereas (*R*,*S*)-diastereoisomer is soluble in water and (*S*,*S*)-diastereomers precipitates (Scheme 2).[9] As soon as the salts are separated, they are treated with acid to obtain the starting ibuprofen as two single enantiomers.

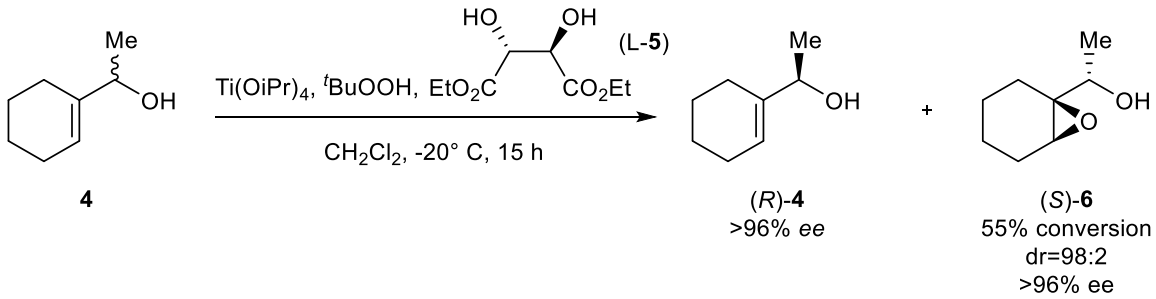


Scheme 2. Chiral resolution of ibuprofen (**1**) using (*S*)-(-)-1phenylethylamine (**2**) as derivatizing agent.

This method is reasonable to use for the compounds which can be quantitatively derivatized as well as quantitatively converted back to the starting materials. The advantages of this type of chiral resolution are the broad substrate scope, relative ease of use and access to both enantiomers after all manipulations in very high enantiomeric purity. However, if only one enantiomer is of interest, which is usually the case, the maximum yield of isolated product is 50%.

Kinetic resolution

In kinetic resolution, one of the enantiomers reacts much faster with a chiral catalyst or reagent than the other one, resulting in an enantioenriched sample of the less reactive enantiomer.[7,10] The enantiomeric excess (*ee)* of the starting material as well as the *ee* of the formed product is directly dependent on the differences in the rate of the reaction between the enantiomers and the resolving agent. Thus, the higher the difference the higher the *ee*. Nowadays a lot of various transformations are used for the kinetic resolution, employing transition metal catalysis, organocatalysis, etc.,[10–13] since it allows to obtain both the products and starting materials in high optical purity from racemates. For example, Sharpless epoxidation is a very reliable method for the kinetic resolution of variety of secondary allylic alcohols (Scheme 3).[14] Implementation of the reaction with (+)-diisopropyl L-tartrate (L-**5**) as a ligand for the titanium catalyst allows to epoxidize selectively only (*S*)-**4** to the give corresponding epoxide (*S*)-**6**, without affecting (*R*)-enantiomer. Both compounds (*R*)-**4** and (*S*)-**6** are obtained in high *ee* of >96%.



Scheme 3. Kinetic resolution of 1-(1-cyclohexen-1-yl)ethanol (**4**) by Sharpless epoxidation with (+)-diisopropyl L-tartrate (L-**5**).

Despite the broad usage, the specificity of these reactions to certain class of substrates and the use of sophisticated catalysts or reagents limit the scope of application.[10,15] In contrast to chiral derivatization, kinetic resolution often allows to obtain only one enantiomer, but there

are at least two possible ways of getting the other one: the use of the other enantiomer of the chiral reagent or conversion of the product to the starting compound by a reaction that preserves the stereochemistry. If the use of another enantiomer of the chiral reagent is not possible, like for example, in enzymatic resolutions[16], or the formed product could not be converted easily to the starting material, access to another enantiomer is hampered. Similar to chiral derivatization, the maximum yield of either isolated product or enantioenriched starting material is 50%. A special case is *dynamic kinetic resolution*,[10,17,18] when the enantiomers can racemize to each other during the process, consuming all the substrate to produce only one product in high *ee*. Therefore, this type of process can also be assigned to the asymmetric synthesis and it will be discussed in the chapter about chiral synthesis.

Preparative chiral chromatography

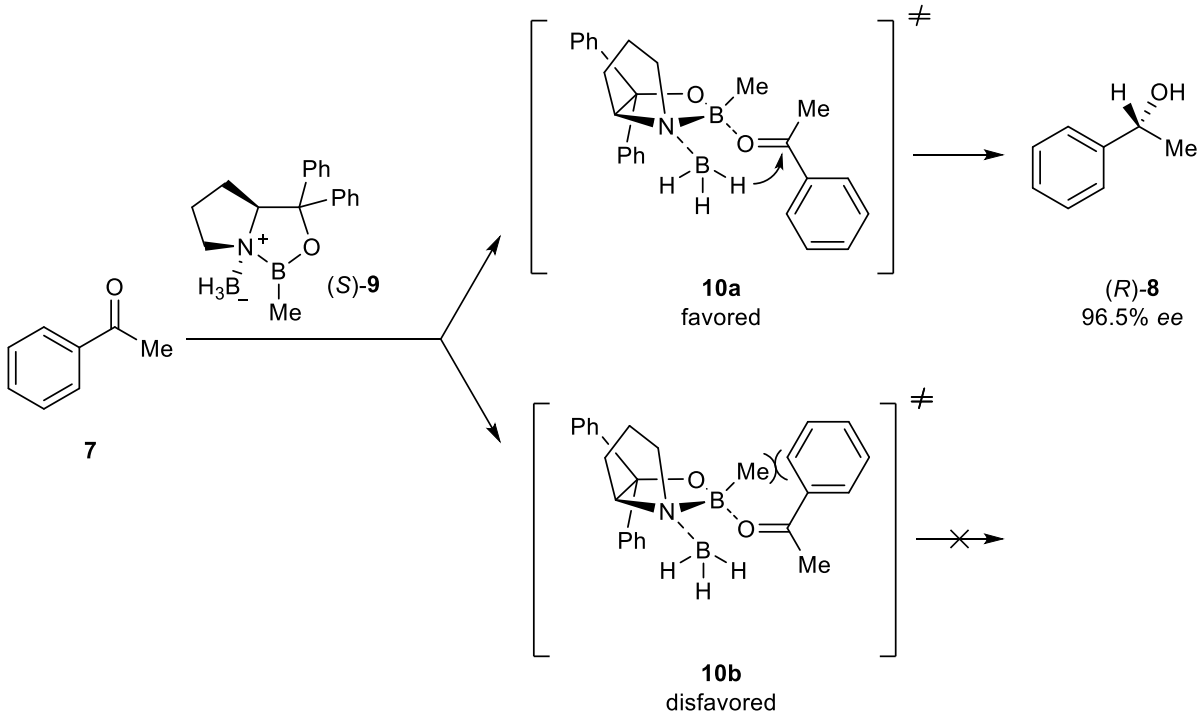
Another important and widely used resolution method is the preparative chiral chromatographic separation.[7,17] It is based on the different ability of enantiomers to interact with the chiral stationary phase and as a result, to separate the racemate. Nowadays many different types of chiral stationary phases are designed according to the chemical structure of the compound and such a great choice of chiral columns makes the chiral chromatography a highly applicable method. For example, racemic mandelic acid has been almost completely resolved by column chromatography on starch.[19] Preparative column chromatography allows to isolate both enantiomers, but if only one is required, the maximum yield of the product is 50%, as in other resolution methods, which is certainly a drawback. Depending on the presence of different functional groups in the racemate, the conditions of the process like different chiral stationary phases, eluents, flow rates, etc. have to be fine-tuned before the resolution method could be used.

Asymmetric synthesis

Since in most of biologically active compounds only one enantiomer is active, it is reasonable to develop methods for the enantioselective synthesis. This type of synthesis is also called asymmetric synthesis.[7] A reaction is enantioselective, if it involves formation of a new chiral element in the target and unequal amounts of enantiomers are produced. According to this definition, the asymmetric synthesis can be divided into several sections: enantioselective catalysis, usage of chiral auxiliaries and chiral pool. All these approaches will be overviewed further.

Enantioselective catalysis

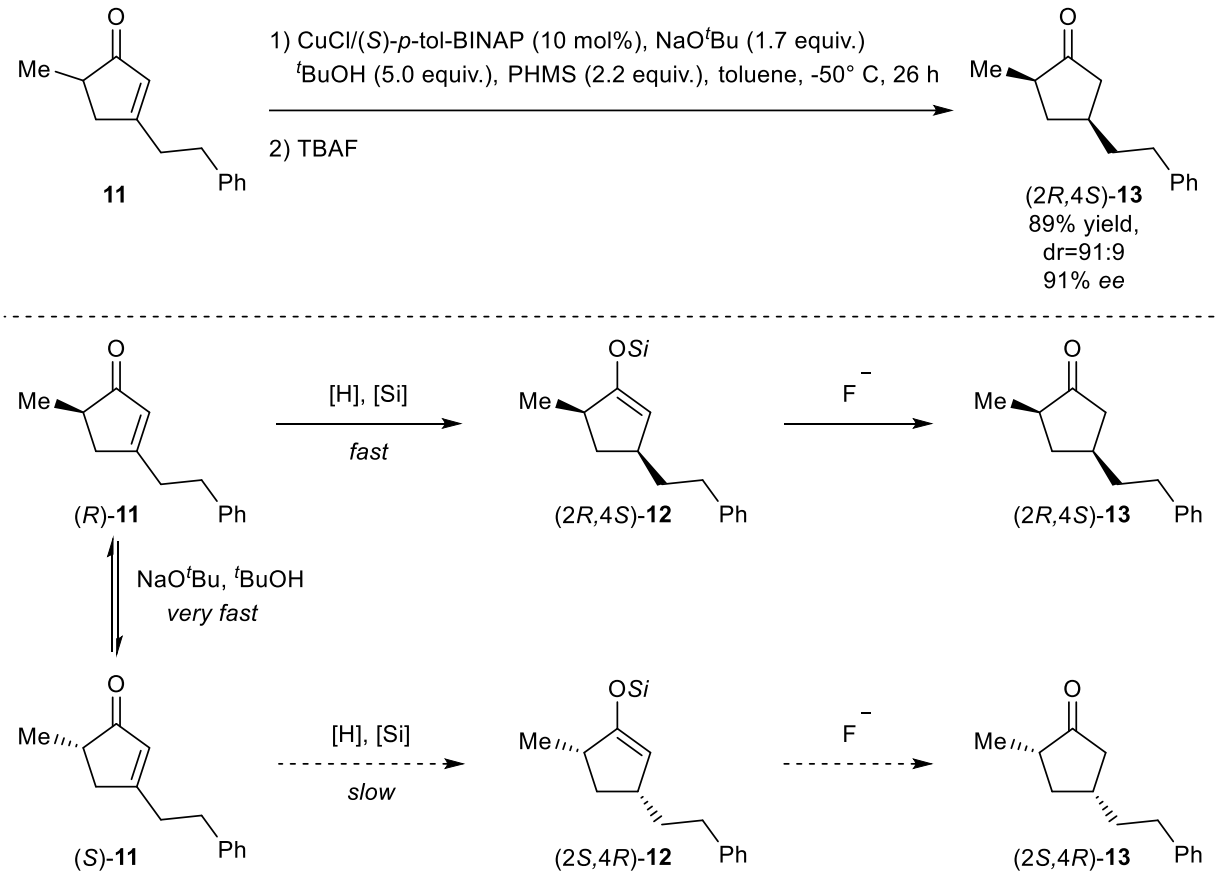
Asymmetric catalysis is a particular case of the field, in which the formation of a chiral centre proceeds employing a chiral catalyst.[7,8,20] Due to the asymmetry of the catalyst, the transition state of reaction is diastereomeric, meaning that the enantiomers have different energetic barriers to complete the reaction. Therefore two pathways of the reaction have different reaction rates, leading to a different enantiomeric ratio of the product. In the ideal case only one chiral transition state could be reached and as a result only one enantiomer could be obtained. Usually, substrates are prochiral or contain a remote chiral functionality, which stays unaffected during the reaction. For example, acetophenone (**7**) could be selectively converted to (*R*)-(+)-phenylethanol ((*R*)-**8**) employing Corey-Bakshi-Shibata reduction (Scheme 4).[21] The (*S*)-oxazaborolidine reacts with BH_3 to produce the active species (*S*)-**9**, which interact with the substrate as a Lewis acid in the least sterically hindered position (**10a**). Since in another transition state methyl group of oxazaborolidine and phenyl group of the ketone are repelling each other (**10b**), this reaction pathway is not favoured. After the coordination, the hydride is transferred to the carbonyl group resulting in ((*R*)-**8**) after the acidic work-up.



Scheme 4. Enantioselective reduction of acetophenone (**7**) to (*R*)-(+)-phenylethanol ((*R*)-**8**) using Corey-Bakshi-Shibata reaction.

A particular case of enantioselective catalysis is dynamic kinetic resolution,[1] which was briefly mentioned before.[10,17,18] Dynamic kinetic resolution is a type of enantioselective reactions between a chiral catalyst and a racemic starting material, which is able to epimerize relatively easily under the reaction conditions. Since enantiomers have different reaction rates with the catalyst and since they can convert to each other faster than the reaction between the less reactive enantiomer and the chiral catalyst occurs, the final product can be formed in 100% *ee* and up to 100% yield. The observed dynamics are based on the Curtin-Hammett principle.[22] Conjugate reduction of 1,4-Michael acceptors with the use of chiral copper catalyst is an example of dynamic kinetic resolution (Scheme 5).[23] In the presence of NaO^{t}Bu/^{t}BuOH the substrate **11** easily epimerizes, producing both enantiomers (*R*)-**11** and (*S*)-**11** in the reaction mixture. The (*R*)-**11** reacts with the catalyst faster than (*S*)-**11**, resulting in the excess of only one of the possible silyl enol ethers (2*R*,4*S*)-**12**. After desilylation with TBAF, the corresponding carbonyl (2*R*,4*S*)-**13** compound was isolated in 89% yield in dr of 91:9 and 91% *ee*.

[1] Since most of the examples of the dynamic kinetic resolution are performed with an asymmetric catalyst, it was decided to classify it here.

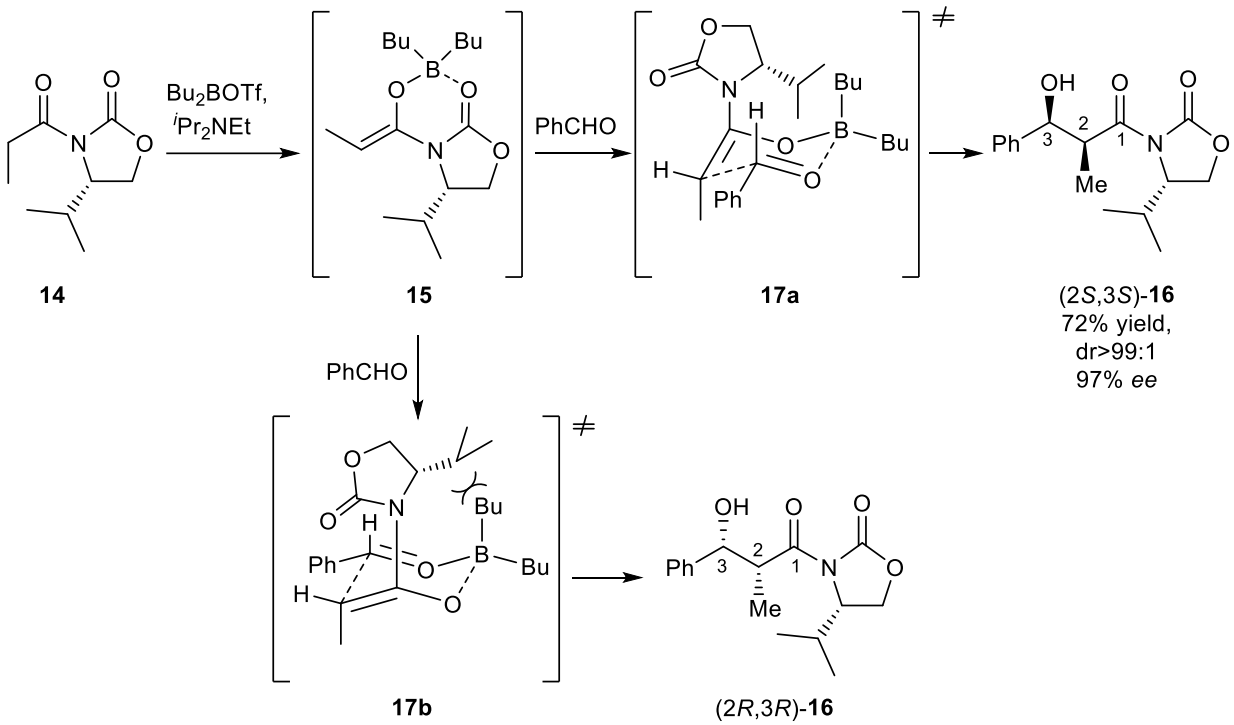


Scheme 5. Dynamic kinetic resolution of Michael acceptor **11** employing enantioselective catalytic conjugate reduction.

Enantioselective catalysis has an enormous impact on the asymmetric synthesis of natural products. Recent progress in organocatalysis, biocatalysis and transition metal chemistry allowed to develop many enantioselective protocols, like asymmetric hydrogenations,[24] Michael additions[25] and aldol reactions,[26] enantioselective epoxidations,[27–29] enantioselective C-H activations and cross-couplings,[8,20] etc.[30] Low loading of chiral catalysts, their commercial availability and possibility to recycle make asymmetric catalysis an especially useful tool to obtain optically pure targets from achiral or racemic starting materials. By selecting an appropriate catalytic system, both enantiomers of the product could be obtained. However, the required catalysts and ligands are complex and expensive. Sometimes the synthesis of a catalyst or a ligand is much more complicated than the products of the performed reaction. Even though some catalytic reactions are well studied and work in highly predictable manner for a broad scope of substrates, some catalysts work only for certain systems. If a new substrate is going to be used, conditions of the reactions have to be optimized accordingly. Due to complexity of the mechanisms of these transformations, it could be difficult to identify any patterns between the stereochemical reaction outcomes, the used chiral catalyst and other conditions. As a result, optimization of the reaction can be problematic.

Chiral auxiliaries

A chiral auxiliary is a chiral group or a unit that is temporarily installed into an organic compound to control the stereochemical outcome of the synthesis.[7,8] The present chirality in the auxiliary directs the stereoselectivity of one or more subsequent reactions. As soon as all chiral transformations are performed, the auxiliary is removed from the target molecule and can be recovered for future use. The most famous examples are the Evans oxazolidinone auxiliaries, that are widely used for the enantioselective aldol reactions,[26,31–33] alkylation reactions,[34,35] Diels-Alder reactions[36,37] and others[33]. In the shown example below, compound **14** reacted with Bu_2BOTf in the presence of base Et_3N to give *Z*-enolate **15** (Scheme 6).[38] The generated enolate **15** was treated with benzaldehyde to exclusively produce *syn*-aldol (*2S,*3*S*)-**16**, which was isolated as a single diastereomer in 97% *ee* and 72% yield. The reaction is proposed to proceed via a Zimmerman–Traxler-type cyclic transition state.[39] The corresponding transition state **17a** is more energetically favorable than **17b** due to steric hindrance of the chiral auxiliary, and as a result only *syn*-(*2S,*3*S*)-**16** was obtained.



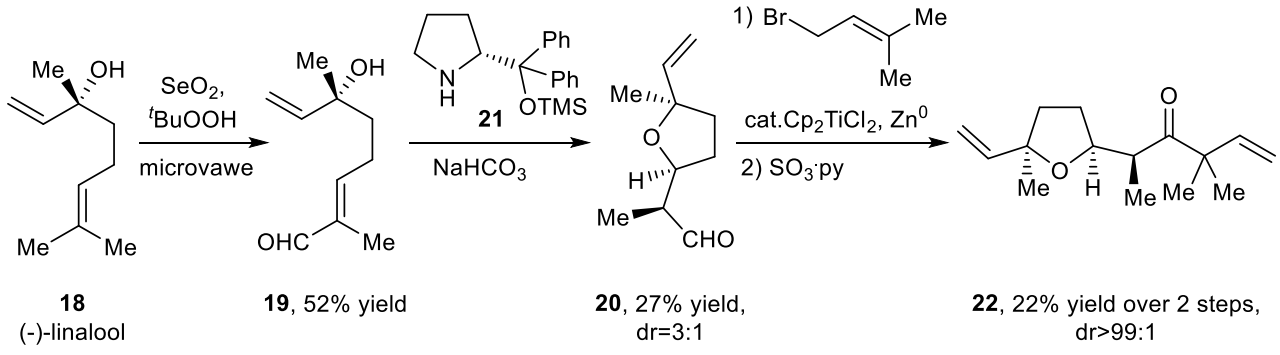
Scheme 6. Asymmetric aldol reaction of compound **14** with benzaldehyde employing the Evans oxazolidinone auxiliary.

Typically chiral naturally occurring compounds, like amino acids, alcohols, etc.[7,8] are used as auxiliaries due to their availability and relative simplicity to install and to remove. In this type of reactions correlations between used auxiliary and the stereochemical outcome are easier determined than in asymmetric catalysis. The stereoselectivity of the transformations is well predictable and the process usually does not require any special optimization. All these aspects make the use of chiral auxiliaries a very reliable method to construct asymmetric molecules. However, there are few drawbacks of the approach. First of all, the introduction and removal of chiral units have to be quantitative and do not disturb any other functionalities in the substrate. The process requires stoichiometric amount of the asymmetric group, which is a big disadvantage in contrast to chiral catalysis. The auxiliary has to be stable under the reaction conditions. Finally, the substrate must have a certain functional group where the chiral moiety could be installed.

Chiral pool

Another approach towards enantiopure targets is a chemical modification of readily available optically active compounds.[7,8] This method is called chiral pool and it is the oldest concept in asymmetric synthesis. In this strategy various stereodefined starting materials are used as building blocks to create more complex molecules. Usually, the available chiral units are

preserved in the synthetic route and the main goal is to avoid their epimerization or other side reactions during the functional group interconversions in the substrate.[40,41] However, in many cases modification of asymmetric atoms could be performed using stereospecific or stereoselective reactions as well. In stereospecific processes the stereochemistry of the reactant completely determines the stereochemistry of the product without any other option. In stereoselective reaction there is a choice of pathway, but the stereoisomer of the product is formed due to the reaction pathway being more favorable than the other ones available. Some existing asymmetric centers could be removed in the synthesis, or in contrast could be used to direct the creation of some new ones. Usually, naturally occurring chiral compounds like amino acids, carboxylic acids, monosaccharides, etc.,[40,41] are used as building blocks. Also, the optically active starting material could be obtained by any other synthetic or resolving method.[40] The synthesis of (+)-artemone from (-)-linalool is a typical example of chiral pool strategy (Scheme 7).[40,42] In the first step the allylic oxidation of (-)-linalool (**18**) was performed under microwave conditions with catalytic SeO_2/^{t}BuOOH, providing the allylic aldehyde **19** in 52% yield. The compound **19** was further converted to the cyclic ether **20** in 27% yield, as a 3:1 mixture of diastereomers, employing the Hayashi−Jørgensen organocatalyst (**21**) and sodium bicarbonate.[43] These conditions promoted *oxy*-Michael addition of the hindered tertiary alcohol to the enal system as well as controlled formation of the α-methyl stereocenter after the protonation of the enolate. In the final step, reverse prenylation of the chiral aldehyde using Ashfeld's conditions[44] took place, and subsequent oxidation led to (+)-artemone (**22**) (22% yield over two steps).



Scheme 7. Total synthesis of (+)-artemone (**22**) from (-)-linalool (**18**) by Vosburg.

Due to the availability of many optically active sources (thanks to Mother Nature and modern synthetic chemistry!), chiral pool approach has found a great application in enantioselective synthesis. Nowadays various synthetic methods allow to convert almost every functionality into another one. This fact encourages synthetic chemists to use chiral pool strategy, since the majority of these reactions do not require a substrate specific optimization of the process.

However, it is always the question of a number of required steps for that transformation and the final yield. Quite often functional interconversion of a structural unit requires many steps and as a result the final yield is low. Also, in some reactions involving transformations of chiral centers, enantioselectivity loss could be observed. The use of a certain available chiral substrate results in formation of only one enantiomer or diastereomer and additional reactions are required.

Conclusion

All of the described methods have certain advantages and disadvantages, which have to be considered when planning a synthetic route to a target. In general, modern separation techniques of racemic mixtures allow to resolve enantiomers completely (up to >99% *ee*) and as a result both enantiomers could be accessed. The maximum yield of the target enantiomer in this case is 50%, therefore, these methods are reasonable to use in the beginning of the synthesis. The asymmetric synthetic strategies allow to obtain the desired enantiomer in quantitative yield. However, in these reactions the control of the stereochemistry could be complicated, and conditions of the process have to be optimized according to the substrate. Also, asymmetric transformations could require many additional steps, like installation and removal of chiral auxiliaries or functional conversions of the substrates in the chiral pool approach. Due to these considerations, chemists combine all these methods to obtain a target and at the end the most suitable route is selected. Imperfection of all these strategies will always force researchers to design new approaches towards the enantioselective synthesis.

Organometallic chemistry

History

Organometallic chemistry is a part of the field studying the compounds containing a carbon-metal bond.[7] The history starts in 1760, when French chemist Cadet discovered the so-called Cadet's fuming liquid, which was one of the products of the reaction between arsenic trioxide (As_2O_3) and potassium acetate.[45] It consisted mostly of dicacodyl $(CH_3)_2AsAs(CH_3)_2$, and cacodyl oxide, $(CH_3)_2AsOAs(CH_3)_2$. Both compounds contain the C-As bond, which is an example of a carbon-metal bond. In the mid-1850s, Frankland prepared a few metal-alkyl compounds, such as diethyl zinc, diethyl mercury, etc., by the insertion of a metal into the carbon halogen bond.[46,47] In 1912, Grignard was awarded the Nobel Price for the discovery of organomagnesium compounds, which had greatly advanced the progress of organic chemistry. The further extensive studies of the synthetic utility of these reagents made them one of the mostly used in organic synthesis.[7,48] In 1917, Schlenk prepared first organolithium compounds – class of organometallic reagents, which are widely exploited for different transformations.[49,50] The first organocopper compound was prepared by Gilman in 1952,[51] giving a start to another important direction of organometallic chemistry. The latest feature is the evolution of the transition metal catalysis. In 2005, R. H. Grubbs and R. R. Schrock were awarded the Nobel Prize for development of the metathesis method in organic synthesis.[52] Later, in 2010, R. F. Heck, E. Negishi and A. Suzuki received the Nobel Prize for the palladium-catalyzed cross couplings.[53] The history of organometallic field is huge and it will never end. Organometallic compounds have an enormous application in synthesis. By selecting certain organometallic species and suitable electrophiles, almost any chemical compound could be prepared. Further general synthetic methods for obtaining these compounds will be discussed, as well as their application in synthesis. Special emphasis would be placed on the chiral organometallic species.

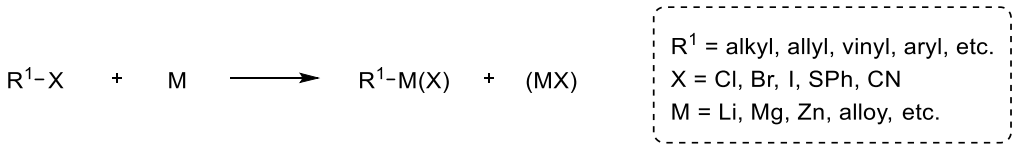
General approaches to organometallic compounds

For a long time, synthetic utility of organometallic chemistry was in the shadows. Carbon-metal bond is polarized and as a result these compounds are reactive.[7,50] Most of organometallics cannot be isolated in pure form, because of easy decomposition. Therefore, they are generated *in situ* or exist as solutions in non-reactive solvents like hexane, diethyl ether, THF, etc. or as stabilized complexes. In case of metalloids like boron, tin, silicon, etc., the corresponding organometallic substances can be isolated, purified and stored since this type of carbon-metal bond is less polarized and as a result more stable.

Due to high ionic character of the carbon-metal bond, configurational stability of chiral organometallics is low and often chiral coordinating groups are required.[50] The epimerization process can be slowed down by treating these reagents at lower temperatures. Also by changing from a highly reactive metal to a less reactive metal, for example, from magnesium to boron, the corresponding organometallic compound will be more configurationally stable.
Synthetic approaches towards the generation of organometallic substances could be divided in few categories: insertion into carbon-heteroatom bond, deprotonation, halogen-metal exchange, transmetalation and carbometalation. The asymmetric organometallics could be obtained in similar way employing chiral starting materials or ligands.

Insertion

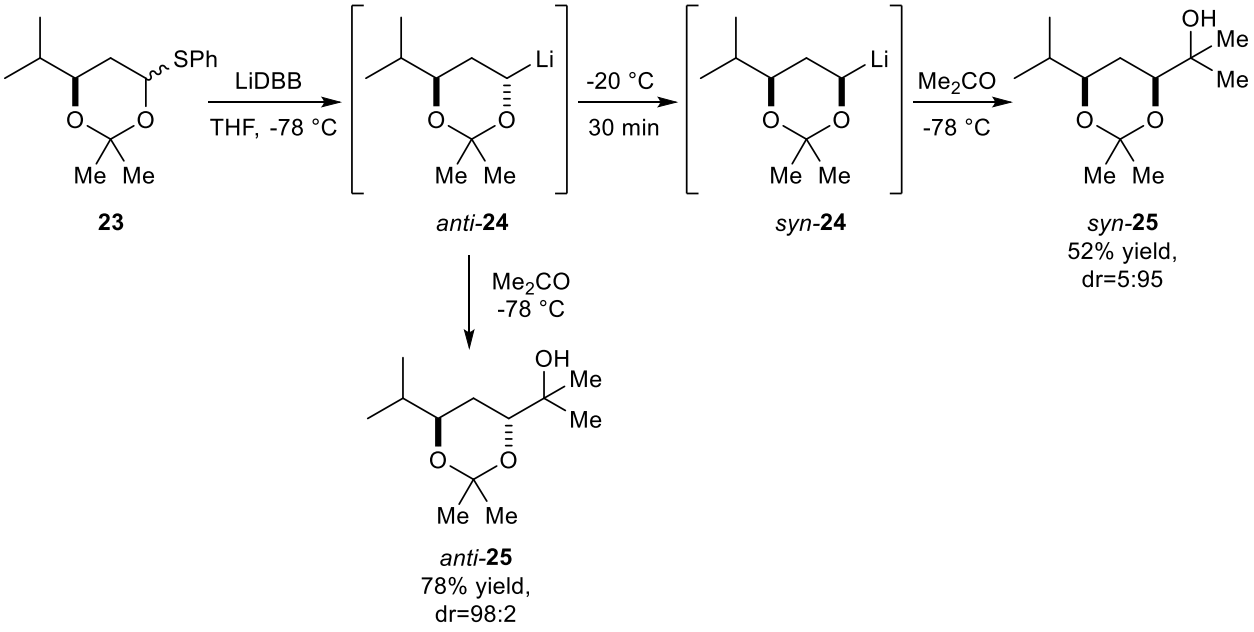
This type of synthesis is based on a reductive insertion of a metal into a carbon-heteroatom bond.[7,50] In contrast to other methods, this one does not require the use of other organometallic reagents. Various alkyl, aryl, vinyl halides (R^1-X) as well as sulphides and nitriles react with elemental metals (M) like lithium, magnesium, zinc, etc., or alloys to obtain the corresponding metallic reagent (R^1-M(X), Scheme 8). [7,50,54–58] A formation of an inorganic salt could also accomplish the reaction, like in case of lithium reagents. The driving force of the process is formation of a thermodynamically highly stable metal-X bond, whereas X is halogens, SPh, etc. The resulting energy benefit compensates the generation of an unstable carbon-metal bond.



Scheme 8. Generation of organometallic compound R^1-M(X) via an insertion of a metal into a carbon-X bond.

Quite often metals are passivated and additional reactants are required to initiate the insertion.[57,58] For example, magnesium turnings can be activated by a reaction with dibromomethane. Some additives, like LiCl, can also facilitate the reaction by the additional stabilization of formed organometallic species. Insertion method is widely used to prepare various organometallic reagents due to the availability of required organic substrates and used metals. Many commercially available organometallic reagents like ^{n}BuLi, ^{t}BuLi, ^{i}PrMgBr, PhMgBr, etc. are prepared via insertion.
Since the process is radical, the organometallic species will always be racemic. However, the certain reaction conditions can favour the formation of one of the possible stereoisomers. Reductive lithiation of thioethers[54,55] and nitriles[56] is used to prepare various asymmetric

organolithiums. For example, thioacetal **23** was converted to the lithium intermediate *anti*-**24** using LiDBB in THF at -78 °C, which subsequently reacted with acetone to produce the corresponding tertiary alcohol *anti*-**25** in 78% yield and dr = 98:2 (Scheme 9). The observed stereochemical outcome of the reaction was explained by the greater stability of the axial radical compared with the corresponding equatorial radical of *anti*-**24** under the kinetic conditions due to anomeric stabilization.[54],[59] However, the lithium agent *anti*-**24** could be completely converted to the corresponding *syn*-**24** derivative at -20 °C within 30 min. The treatment of *syn*-**24** with acetone provided tertiary alcohol *syn*-**25** in 52% yield and dr = 5:95. The changed conditions allowed to selectively obtain *syn*-**24** lithium intermediate, which is considered to be more thermodynamically stable since the lithium atom is in equatorial position.[54]

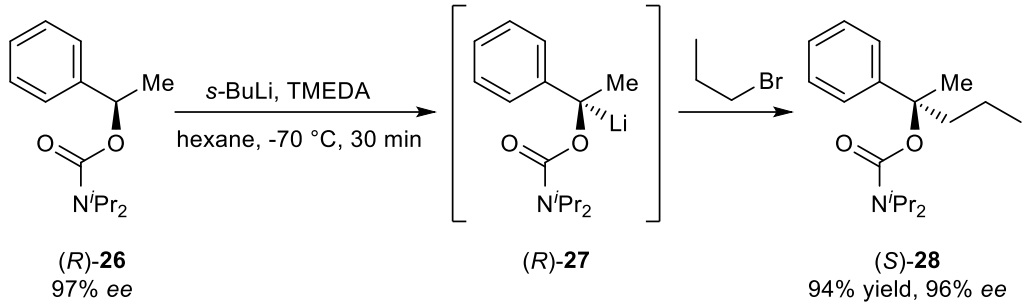


Scheme 9. Generation of alkyllithiums *anti*- and *syn*-**24** via reductive lithiation of thioacetal **23** and subsequent reactions with acetone, leading to the corresponding alcohols *anti*- and *syn*-**25**.

Deprotonation

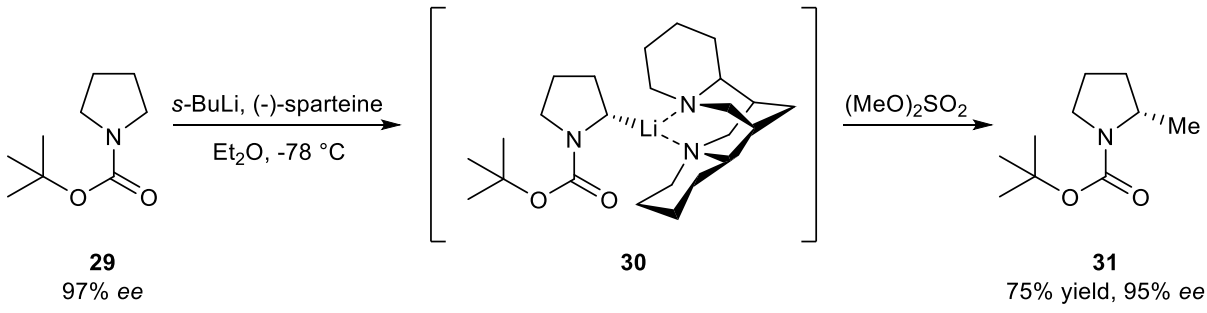
Another way to synthesize an organometallic compound is a deprotonation – a reaction between a C-H acid and a metallic base. This method is based on an acid-base equilibrium. Coordinating groups like amines, ethers, and others, as well as electron-withdrawing substituents, like halogens, carbonyls, etc., can increase the stability of the formed carbon-metal bond and therefore shift the equilibrium towards the metalated species.[7,50,60–62] Various organometallics can be used as a base, for example, ^{n}BuLi or ^{i}PrMgBr, however, amino-derived bases like LDA and TMP bases,[63] are applied more frequently.

Many chiral organometallics are generated by deprotonation. Chirality could be preserved by the use of chiral coordinating groups or neighbouring substituents in a substrate.[50,64–66] For example, (*R*)-**26**, (97% *ee*) can be selectively deprotonated by a mixture of ^{s}BuLi and TMEDA in hexane at -78 °C to produce α-oxygen stabilized chiral lithium reagent (*R*)-**27** (Scheme 10).[64] The treatment of (*R*)-**27** with *n*-propyl bromide provides the corresponding alkylated product (*S*)-**28** in 94% yield and 96% *ee*.



Scheme 10. Generation of alkyllithium (*R*)-**27** via deprotonation of (*R*)-**26** with *s*-BuLi and TMEDA and subsequent alkylation with *n*-propyl bromide to provide (*S*)-**28**.

Another way to control the configuration is an addition of chiral ligands, such as sparteine.[61],[67] For example, *s*-BuLi deprotonates *N*-Boc-pyrrolidine (**29**) in diethyl ether at -78 °C in the presence of (-)-sparteine to form the lithiated product **30** (Scheme 11).[60] Due to the complexation with (-)-sparteine, the lithium species (**30**) are obtained as a single enantiomer. The following methylation with $(MeO)_2SO_2$ provided the compound **31** in 95% *ee* and in 75% yield.



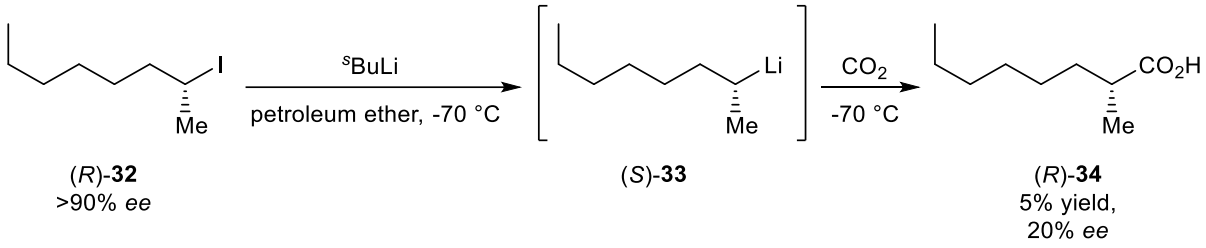
Scheme 11. (-)-Sparteine-controlled deprotonation of *N*-Boc-pyrrolidine (**29**) and subsequent trapping with $(MeO)_2SO_2$ to obtain **31**.

Halogen-metal exchange

Halogen-metal exchange is a common way to synthesize many organometallic reagents.[7,50] The driving force of this process is a formation of a more stable organometallic. The

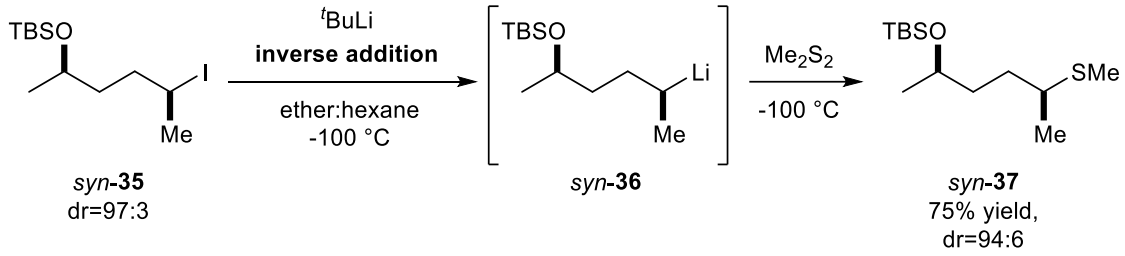
stabilization could be achieved by additional complexation or withdrawing inductive effects, for example, changing an sp^3 carbon atom to sp^2. The halogen-metal exchange is a reversible reaction and the removal of the formed organic halide from the reaction mixture will facilitate the desired exchange. The mechanism of the exchange is strongly dependent on the nature of the species.[68–70] For example, lithiation of aromatic bromides and iodides goes through the formation of "ate"-complexes. Bromide-lithium exchange of secondary substrates is radical, whereas the lithiation of secondary iodides can proceed via radical or polar mechanisms. It was shown, that higher temperatures and coordinating agents favor the radical pathway in the iodide-lithium exchange of secondary substrates.[70]

The chiral iodine-lithium exchange was first made by Letsinger (Scheme 12).[71] He performed an addition of ^{s}BuLi to alkyl iodide (*R*)-**32** at -70 °C in petroleum ether over two hours to generate alkyllithium (*S*)-**33**. After quenching the organolithium reagent (*S*)-**33** with CO_2, he isolated the corresponding carboxylic acid (*R*)-**34** in 5% yield and 20% *ee.* Apparently, the lithium species (*S*)-**33** racemized rapidly under the reaction conditions. Such a low yield could be explained by the side reactions such as elimination and deprotonation.



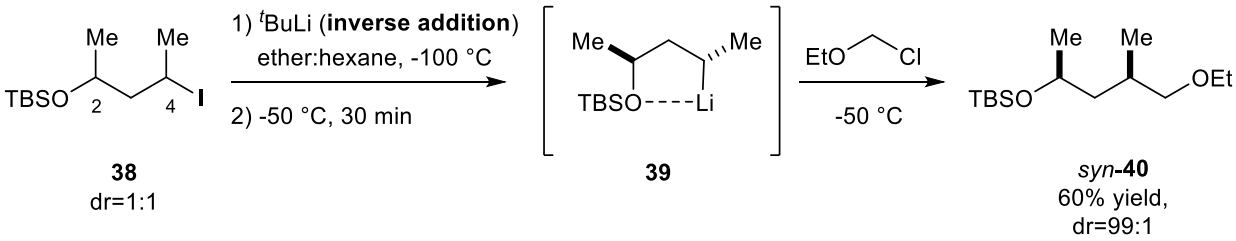
Scheme 12. Iodide-lithium exchange of (*R*)**-32** using ^{s}BuLi and following trapping with CO_2 to obtain carboxylic acid (*R*)**-34**.

Recently, Knochel and co-workers developed a new procedure of the iodine-lithium exchange of chiral secondary species.[72–74] An addition of a solution of an alkyl iodide to a solution of ^{t}BuLi at -100 °C in the mixture of hexane:ether allowed to decrease the elimination and deprotonation side reactions and to generate corresponding alkyllithiums in high yield with a high retention of configuration. For example, alkyl iodide *syn*-**35** was converted to the corresponding lithium reagent *syn*-**36** with the retention of configuration using ^{t}BuLi and an inverse addition of the iodide (Scheme 13).[73] The subsequent trapping of the alkyllithium *syn*-**36** with Me_2S_2 provided thioether *syn*-**37** in 75% yield and dr = 94:6. The stereochemical outcome of the reaction was confirmed by a reaction of the iodide *anti*-**35** with MeSNa, which proceeds with the inversion of configuration and provides the thioether *syn*-**37**.[73]



Scheme 13. Iodide-lithium exchange of alkyl iodide *syn*-**35** to obtain alkyllithium *syn*-**36** and its quenching to provide thioether *syn*-**37**.

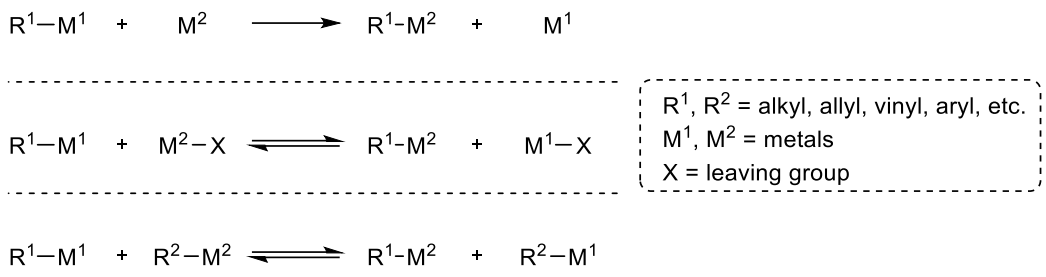
Various asymmetric alkyl iodides can be converted to the corresponding unstabilized alkyllithiums with retention of configuration.[72–74] However, an interesting case of a convergent iodide-lithium exchange was reported (Scheme 14).[74] In this case, a diastereomeric mixture of 2-OTBS substituted alkyl iodides **38** was lithiated employing the inverse addition of ^{t}BuLi at -100 °C. After keeping the reaction mixture at -50 °C for 30 min, only one diastereomer **39** was exclusively formed. The observed convergence is a result of the formation of a five-membered cyclic intermediate due to the intramolecular coordination of a lithium atom to an oxygen atom (**39**). Quantum chemical calculations showed that steric hindrance between the methyl groups favors the formation of **39**.[74] After the alkylaltion of **39**, the compound *syn*-**40** was obtained in 60% yield as a single diastereomer.



Scheme 14. Stereoconvergent generation of alkyllithium **39** and subsequent alkylation to yield *syn*-**40**.

Transmetalation

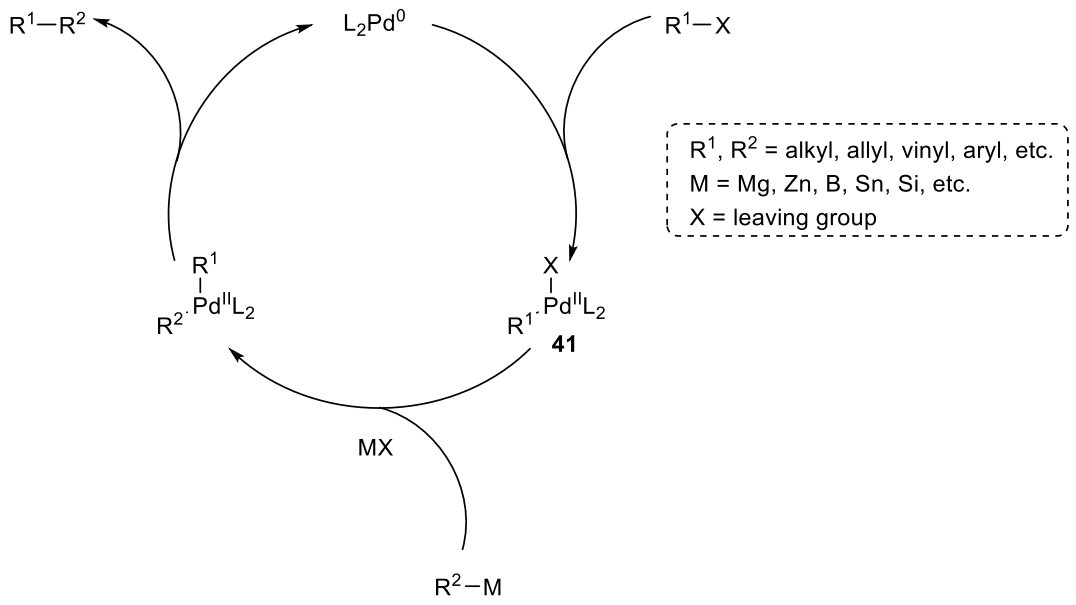
Probably, transmetalation is the most common way to synthesize various organometallic reagents. This method requires a use of two metal-containing compounds, resulting in the exchange of the metal atoms. The exchange can be achieved by an elemental metal, a salt or another organometallic reagent (Scheme 15).[7,50]



Scheme 15. General transmetalation methods to obtain new organometallics.

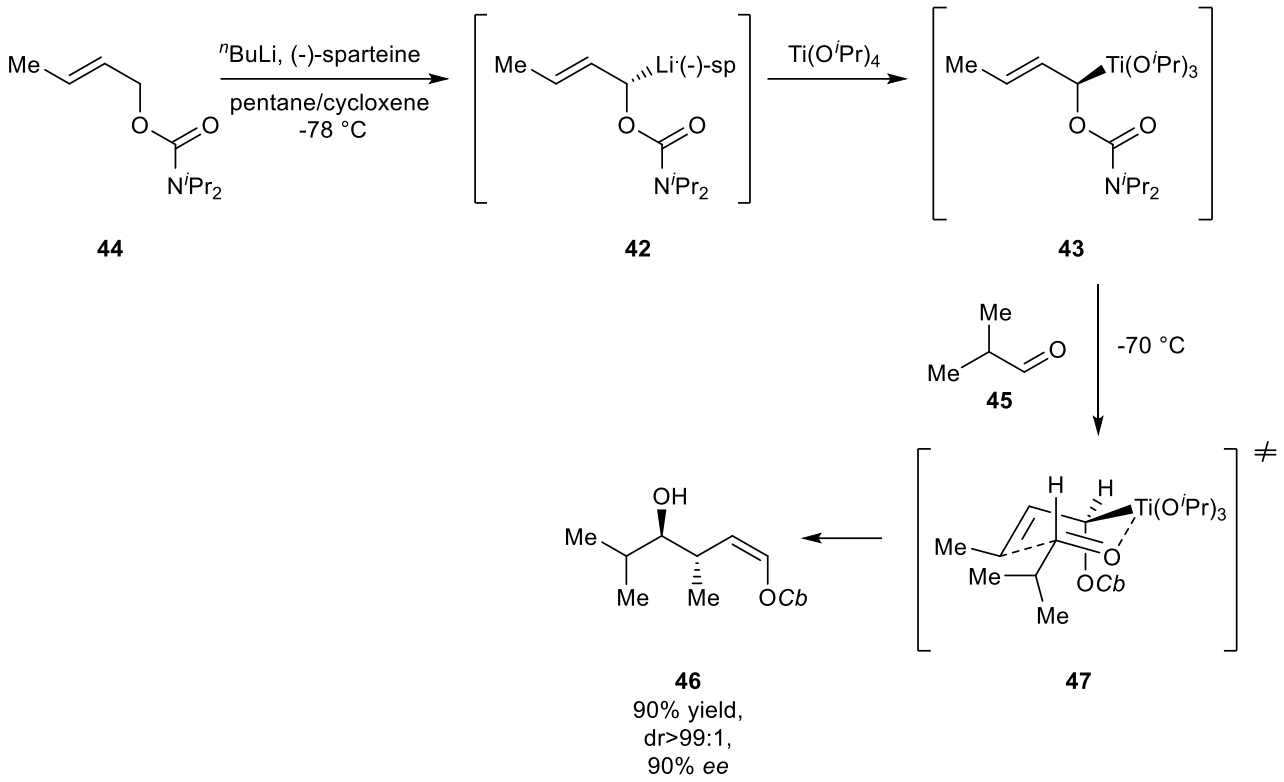
In the first case (Scheme 15, top), M^2 acts as a reducing agent to R^1-M^1, producing M^1 as an elemental metal and a new organometallic species R^1-M^2. The metal M^2 has to be above M^1 in the reactivity series, otherwise, the process will not be energetically favoured.[7] The new organometallic (R^1-M^2) stays in the reaction mixture and the precipitated metal (M^1) can be relatively easily removed from the system. This method is rarely used in the research laboratories for the synthesis, but it is the only ensured technique to prepare various halogen-free metalorganic species.[7] Due to radical nature of the transformation, this type of transmetalation is not used for making chiral organometallics.

The next process is a reaction between organometallic species (R^1-M^1) and a transmetalating reagent (M^2-X), for example, metal halides or other salts (Scheme 15, middle). The driving force of this process is a formation of a more covalent carbon-metal bond and a more ionic salt.[7,50] The reaction can be reversible, as for example, the Schlenk equilibrium for the organomagnesium reagents.[75,76] The equilibrium can be shifted by the precipitation of the formed salt. This transmetalation technique is widely used in the research laboratories, because it allows to synthesize a variety of organometallics, like organocoppers,[77,78] organozincs,[78] etc., from easily accessible Grignard- or lithium reagents. For example, this type of transmetalation takes place in the palladium catalysed cross-couplings, providing the key palladium intermediate (**41**, Scheme 16).[53] As R^2-M there could be used various organometallic reagents, like organomagnesium (Kumada-Corriu), organozinc (Negishi), organotin reagents (Stille).



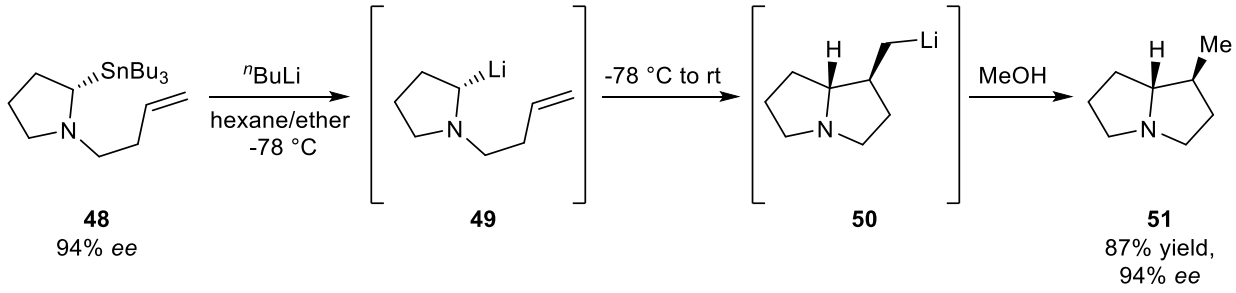
Scheme 16. Catalytic cycle of the Pd-catalysed cross-couplings using organometallic reagents.

This type of the transmetalation is widely used to obtain chiral organometallic species. For example, chiral alkyllithium **42** can be transmetalated to the corresponding alkyltitanium reagent **43** (Scheme 17).[50,61,79] The lithium reagent **42** was obtained by the deprotonation of **44** with ^{s}BuLi in the presence of (-)-sparteine, which was discussed earlier. The allyl lithium **42** was converted to allyltitanium reagent **43** with the complete inversion of configuration,[61] employing Ti(O^{i}Pr)$_4$ as a transmetalating agent. The obtained chiral titanium species reacted with aldehyde **45** to form chiral alcohol **46** in 90% yield, dr>99:1 and 90% *ee*.[79] The observed diastereomeric ratio is due to the Zimmerman-Traxler transition state (**47**) of the reaction between allyltitanium reagent **43** and aldehyde **45**. The inversion at the asymmetric center during the transmetalation in this case is the result of the allyl-stabilization of chiral lithium reagent **42**.[61,79] Depending on the nature of the starting chiral organometallic, transmetalation as well as trapping with other electrophiles can proceed with the inversion or retention of configuration. These details will be discussed in another chapter.



Scheme 17. Transmetalation of asymmetric lithium **42** to the corresponding titanium **43** and subsequent reaction with aldehyde **44**.

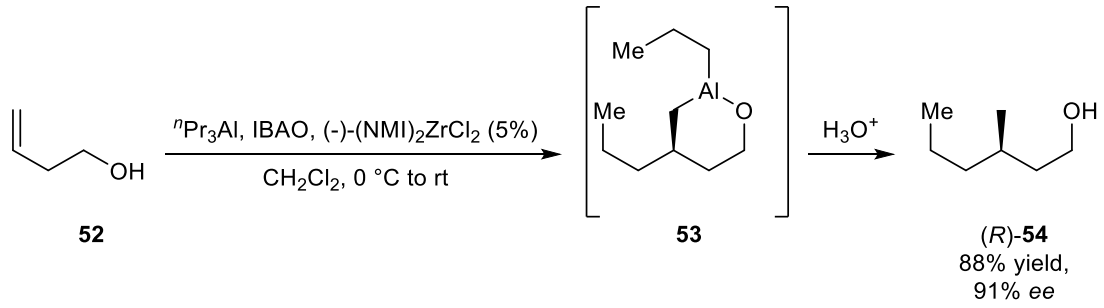
The bottom reaction in Scheme 15 represents a ligand exchange of two organometallic reagents.[7,50] This process is reversible and various reaction conditions as well as the nature of ligands will shift the equilibrium accordingly. This type of the transmetalation is actively used to obtain chiral lithium compounds from corresponding organotin compounds.[61,80,81] For example, tin compound **48** is selectively transmetalated to the corresponding lithium intermediate **49** with the retention of configuration using ^{n}BuLi at -78 °C (Scheme 18).[81] During the warm up to room temperature, an intramolecular cyclization occurred, providing primary alkyllithium **50**. The lithium intermediate **50** was subsequently treated with methanol to furnish compound **51** in 87% yield and 94% *ee*.



Scheme 18. Transmetalation of asymmetric alkyltin **48** to the corresponding alkyllithium **49** and subsequent cyclisation to provide **51**.

Carbometalation

Carbometalation is a reaction between an organometallic reagent and another compound resulting in the formation of a new organometallic compound, which is more energetically favourable under the reaction conditions.[82–85] The formed metallic species can be stabilized by intramolecular coordination, various electronic effects or other factors, which were mentioned earlier. An example of intramolecular lithium carbometalation was mentioned in Scheme 18. The secondary alkyllithium **49** adds to the double carbon-carbon bond to generate primary alkyllithium **50** which is more stable. The subsequent quenching of the metalorganic **50** with MeOH led to compound **51**. The ZACA reaction is also a typical example of enantioselective carbometalation (Scheme 19).[82,83] The mechanism of this reaction is not fully understood and it is supposed to proceed via the enantioselective addition of zirconium species to the unsaturated carbon-carbon bond of the alkene (**52**) and subsequent transmetalation to the organoaluminium compound of type **53**. The obtained alkyl aluminium intermediate further reacted with an acid to provide chiral alcohol (*R*)-**54** in 88% yield and 91% *ee*.[82,86]

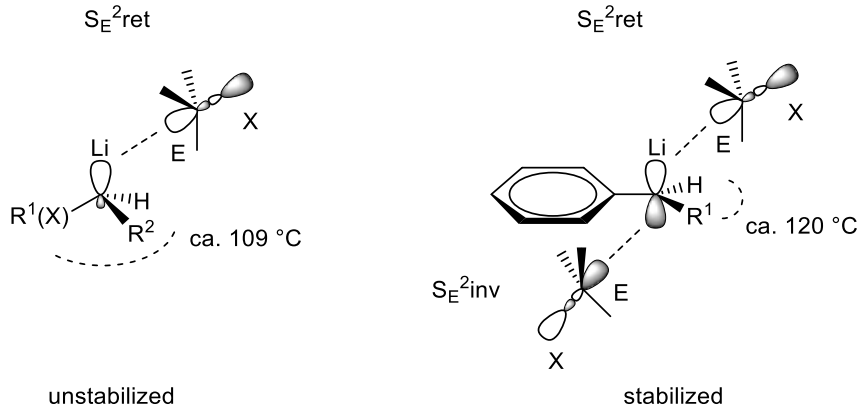


Scheme 19. Enantioselective carboalumination of **52** using ZACA reaction to obtain (*R*)-**54**.

Stereochemistry of organometallics in reactions with electrophiles

A majority of chiral organometallics, like lithium-, copper-, titan-containing species, react with the retention of configuration (Schemes 10-13, 18).[50,61,73,78] However, in some cases (Scheme 17), the inversion of configuration is observed.[61] Since most of organometallics are not accessible in pure form, it is difficult to say when the inversion occurs: either when they are generated or when they react with electrophiles.

The reasons why some chiral organolithiums react with the inversion and some with the retention of configuration are not clear, however, there are some trends[50,61,64] As a rule of thumb, the retentive trapping is observed for unstabilized alkyllithiums like **33** and **36** (S_E^2ret mechanism, Scheme 20).[50,61,64,72–74] Because the unstabilized species are tetrahedral, the attack could happen only from one side, resulting in the retention of configuration. Stabilized lithium species, like benzylic and allylic, can react both with the inversion and the retention of configuration.[61] Due to conjugation, the C-Li bond has more p-character, therefore, the species are planar and the attack of the electrophile could occur from both sides (S_E^2ret and S_E^2inv, Scheme 20).



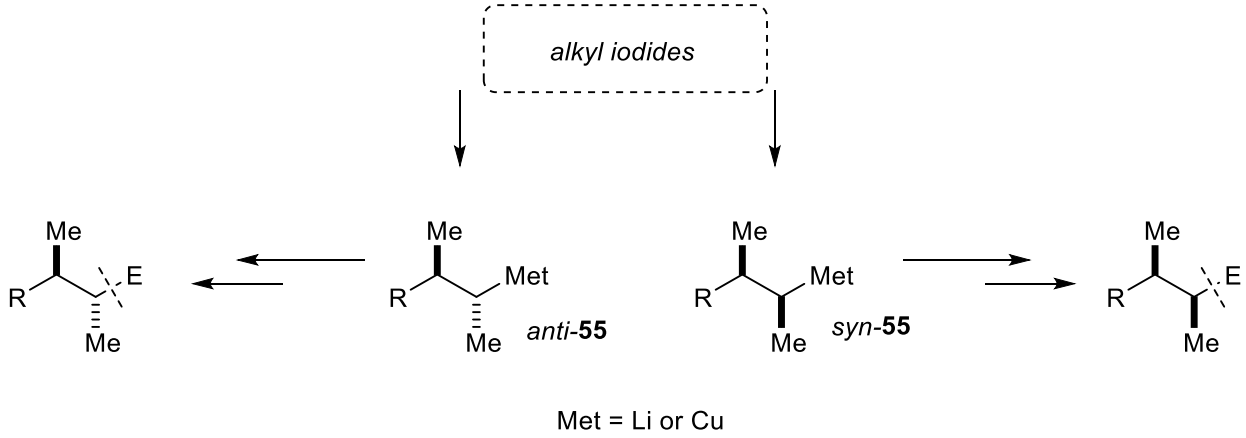
Scheme 20. Frontier orbitals in the reaction of alkyllithiums with electrophile (E-X).

Conclusion

Chiral organometallics can be synthesized in many ways. The stereochemistry of these formed species can be controlled in different manners, as by using the chiral starting material or asymmetric ligands. Various other factors, like intramolecular coordination or electronic inductive effects, could also influence the stereoselectivity. Different asymmetric organometallics react with various electrophiles either with retention or with inversion of configuration and the outcome strongly depends on the nature of the used species. However, the handling of these organometallics can be complicated, and, in many cases, the configurational stability is low. Various organometallics react with different substrates, providing a great diversity of formed products. The use of both a chiral metalorganic reagent and a matching reaction partner can allow to synthesize complex molecules with more than one stereocenter. As was shown before, the chiral organometallic (Scheme with titan) can direct the side of the reaction, which leads to a creation of a new asymmetric centre. Therefore, detailed study of the synthesis, stability and subsequent reactions of chiral organometallics with various electrophiles are of high importance.

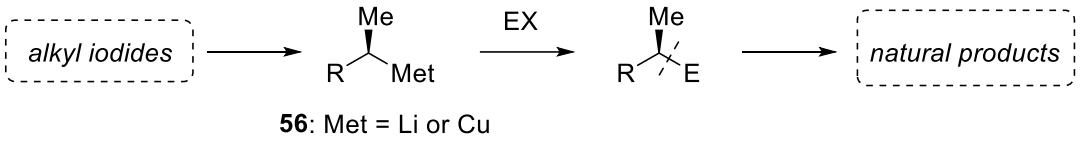
Objectives

The aim of the first part of the thesis was the development of a convenient method to synthesize chiral secondary alkyllithiums and alkylcoppers of type **55** and to study their reactivity towards various electrophiles (Scheme 21).



Scheme 21. The *anti*- and *syn*-alkyl organometallics **55**.

The second goal of my thesis was to synthesize optically alkyl organometallics of type **56** and study their configurational stability. Due to high importance of enantioselective synthesis, I also wanted to explore the synthetic scope of these organometallics and to apply the methodology to the total synthesis of biologically active compounds.



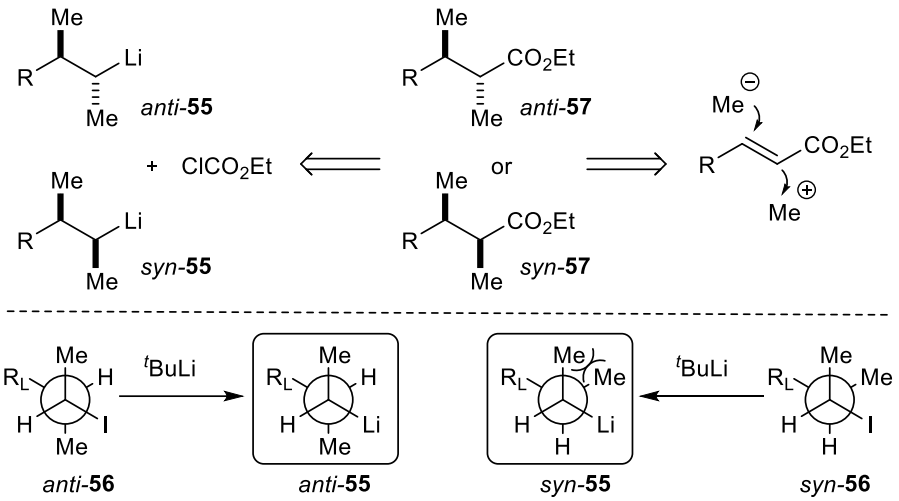
Scheme 22. The alkyl chiral organometallics **56**: synthesis and further application.

Results and discussion

Stereoselective Synthesis and Retentive Trapping of α-Chiral Secondary Alkyllithiums Leading to Stereodefined α,β-Dimethyl Carboxylic Esters

The preparation of chiral organometallic building blocks is useful for the stereoselective construction of acyclic natural products bearing several adjacent chiral centers.[8,50,85] For example, the diastereoselective synthesis of 2,3-dimethylcarboxylate derivatives of type **57** encountered in complex natural products[87–89] may be performed using a diastereoselective 1,4-addition/alkylation. This retrosynthesis has been often used, but has several drawbacks such as the level of the diastereoselectivity and an inability to access both *anti*- and *syn*-isomers **57.** Alternatively, one can envision to use a carboxylation of the chiral organolithium reagents of type **55** with $ClCO_2Et$ for a stereoselective preparation of esters of type **57** (Scheme 23). Although acyclic heteroatom-stabilized chiral lithium reagents are well known, as was discussed in the introduction, non-stabilized secondary alkyllithiums have been less extensively studied.

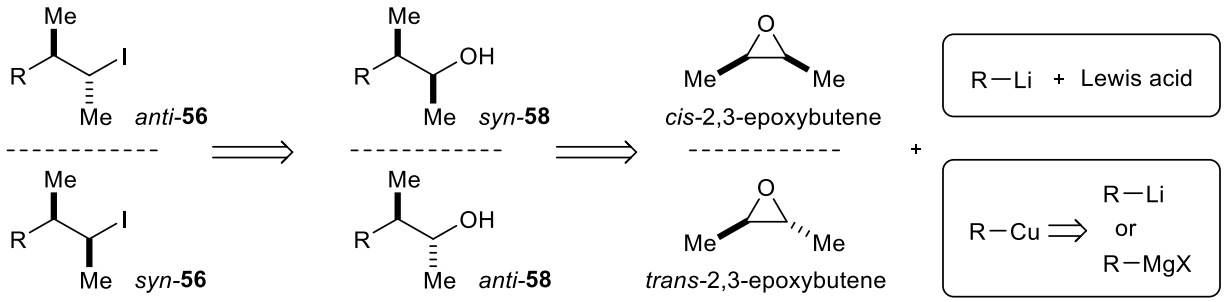
In this chapter, a highly stereoselective preparation of various α-chiral alkyllithiums of type **55** starting from the corresponding iodides and their application to the stereoselective preparation of 2,3-dimethylcarboxylates of type **57** will be discussed. As shown by Newman's projections of α-chiral alkyllithiums of type **55**, steric hindrance between the methyl groups exists in the *syn*-**55** organolithium compounds which makes them less configurationally stable than *anti*-**55** alkyllithiums and the obtained results will be compared with this hypothesis (Scheme 23).



Scheme 23. The retrosynthetic analysis of *anti*- and *syn*-2,3-dimethyl-carboxylate derivatives (**57**), and diastereoselective generation of α-chiral *anti*- and *syn*-secondary alkyllithiums (**55**) from the secondary alkyl iodides (**56**).

Synthesis of the *anti*- and *syn*-secondary iodides (56)

Various secondary *anti*- and *syn*- alkyl iodides **56** were prepared from the corresponding *syn*- and *anti*-alcohols of type **58** using the Appel reaction, which proceeds with the inversion of configuration.[73,90] The majority of the corresponding *syn*- and *anti*-alcohols of type **58** can be easily synthesized using *cis*-2,3-epoxybutane or *trans*-2,3-epoxybutane and suitable metalorganic reagent (Scheme 24).[91–93]



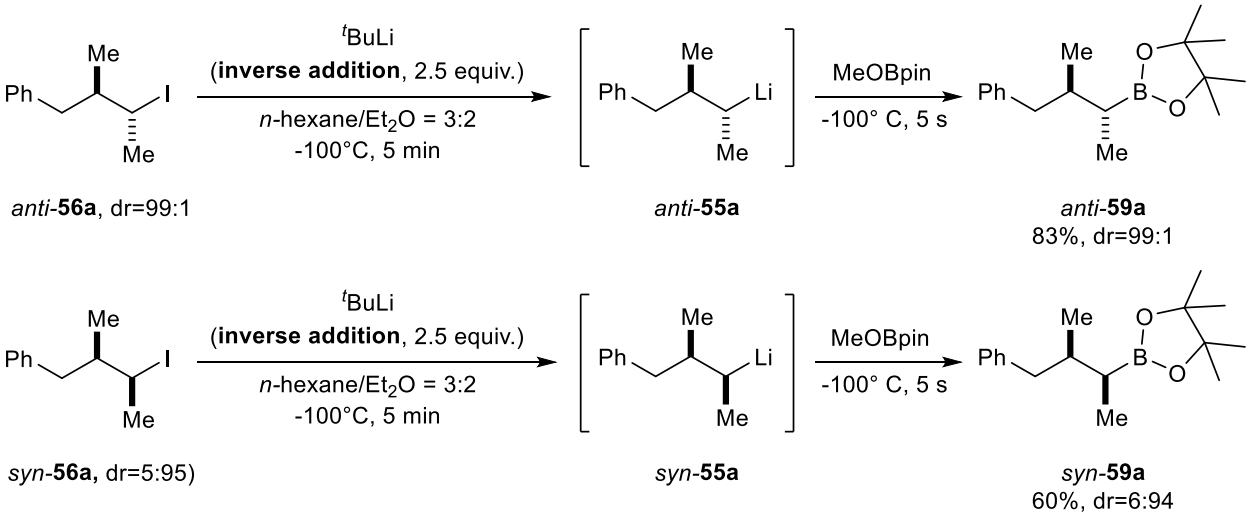
Scheme 24. The retrosynthetic analysis of *anti*- and *syn*- alkyl iodides (**56**).

One common procedure of the epoxide opening reaction involves an organolithium reagent and equimolar amounts of Lewis acid, for example, $BF_3 \cdot Et_2O$ complex, which coordinates to the epoxide and increases its electrophilicity.[91] Another important alternative is a use of organocopper reagents.[92] The corresponding organocopper reagents can be generated *in situ* from various organolithium or Grignard reagents and a transmetalating copper reagent. However, in our experience, the second method – via organocopper reagent – has broader

reaction scope and better yields. In some other particular cases *syn*- and *anti*- alcohols were prepared using other specific synthetic strategies and it is fully described in the experimental part.

Electrophile scope

Thus, the treatment of diastereomerically enriched *anti*-alkyl iodide (*anti*-**56a**, dr=99:1) with ^{t}BuLi, performing an inverse addition in the solvent mixture of hexane:ether (3:2) at -100°C in 5 min, provides the intermediate lithium reagent (*anti*-**55a**). This alkyllithium (*anti*-**55a**) was trapped with MeOBpin[73,74] (2 equiv. -100° C, 10 s) leading to the *anti*-boronic ester (*anti*-**59a**) in 83% yield and with dr=99:1, showing a high retention of the configuration.[73] Similarly, the reaction of the other diastereomer *syn*-**56a** (dr=5:95) with ^{t}BuLi under the same conditions followed by a quenching with MeOBpin gives the *syn*-boronic ester (*syn*-**59a**) in 60% yield and dr=6:94, indicating again a high retention for this electrophilic substitution (Scheme 25). X-Ray diffraction analysis of *syn*-boronic ester (*syn*-**59a**) showed the *syn* position of the methyl groups (Figure 1), which confirms that the whole reaction sequence (I/Li–exchange and subsequent trapping with electrophile) proceeds with retention of the configuration. When the formed lithium reagent *anti*-**55a** was extra stirred for 30 min at -50 °C and then reacted with the MeOBpin, the diastereomeric ratio of the products *anti*-**59a** to *syn*-**59a** was 66:34 compared to 99:1, derived from the experiment with the direct quench with the electrophile.



Scheme 25. Stereoselective preparation of *anti*- and *syn*-boronic esters (*anti*-**59a** and *syn*-**59a**) from corresponding *anti*- and *syn*-alkyl iodides (*anti*-**56a** and *syn*-**56a**) via I/Li-exchange and subsequent trapping with MeOBpin.

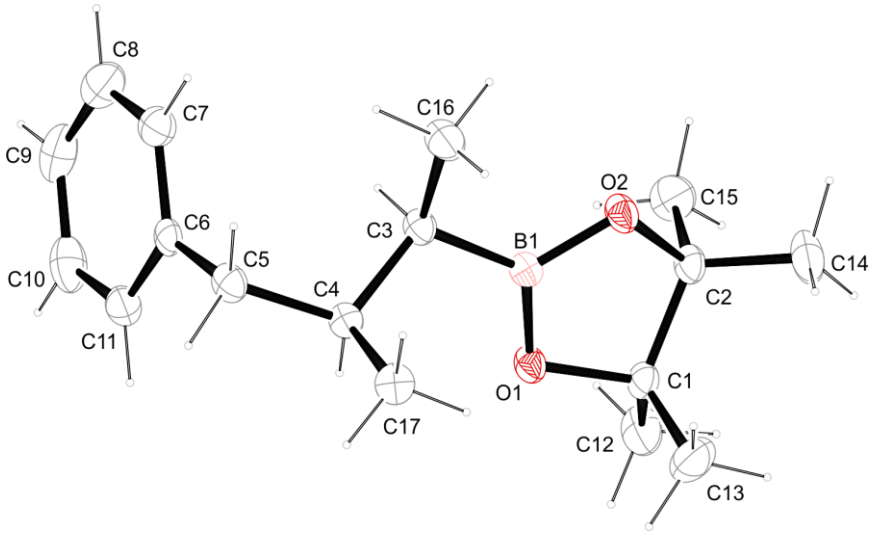
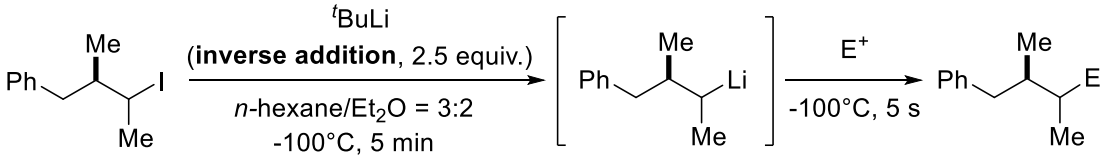


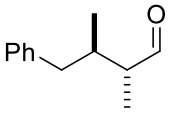
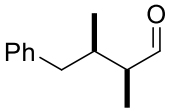
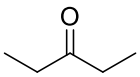
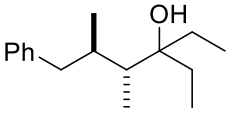
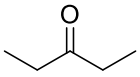
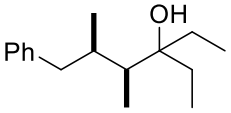
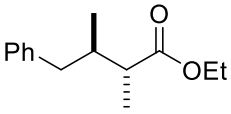
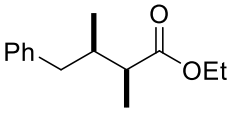
Figure 1. X-Ray structure of *syn*-boronic ester (*syn*-**59a**).

This reaction sequence was extended to other electrophiles. Reactions of the lithium reagents *anti*-**55a** and *syn*-**55a** with DMF[73,74] produced the corresponding *anti*- and *syn*-aldehydes (*anti*-**59b** and *syn*-**59b**, entries 1 and 2 of Table 1) in 60-70% yield with 93-95% retention of configuration. The tertiary alcohols *anti*-**59c** (dr=97:3, 71% yield) and *syn*-**59c** (dr=8:92, 50% yield) were prepared by the addition of alkyllithiums *anti*-**55a** and *syn*-**55a** to Et_2CO (entries 3 and 4 of Table 1).[54,73,74,94] Most importantly, the use of $ClCO_2Et$[73,74] as an electrophile in this sequence afforded the ethyl 2,3-dimethylcarboxylic esters *anti*-**57a** (dr=97:3) and *syn*-**57a** (dr=9:91) in 75-82% yields (entries 6 and 5 of Table 1). In all cases, high levels of retentive substitutions were found (> 94% retention), however the better diastereoselectivity was observed for the *anti*-**59**,**57a** products than for the corresponding *syn*-**59**,**57a** products.

Table 1. Diastereoselective reactions of *anti*- and *syn*- acyclic secondary alkyllithiums **55a** with electrophiles leading to products of type **59** and **57a**.



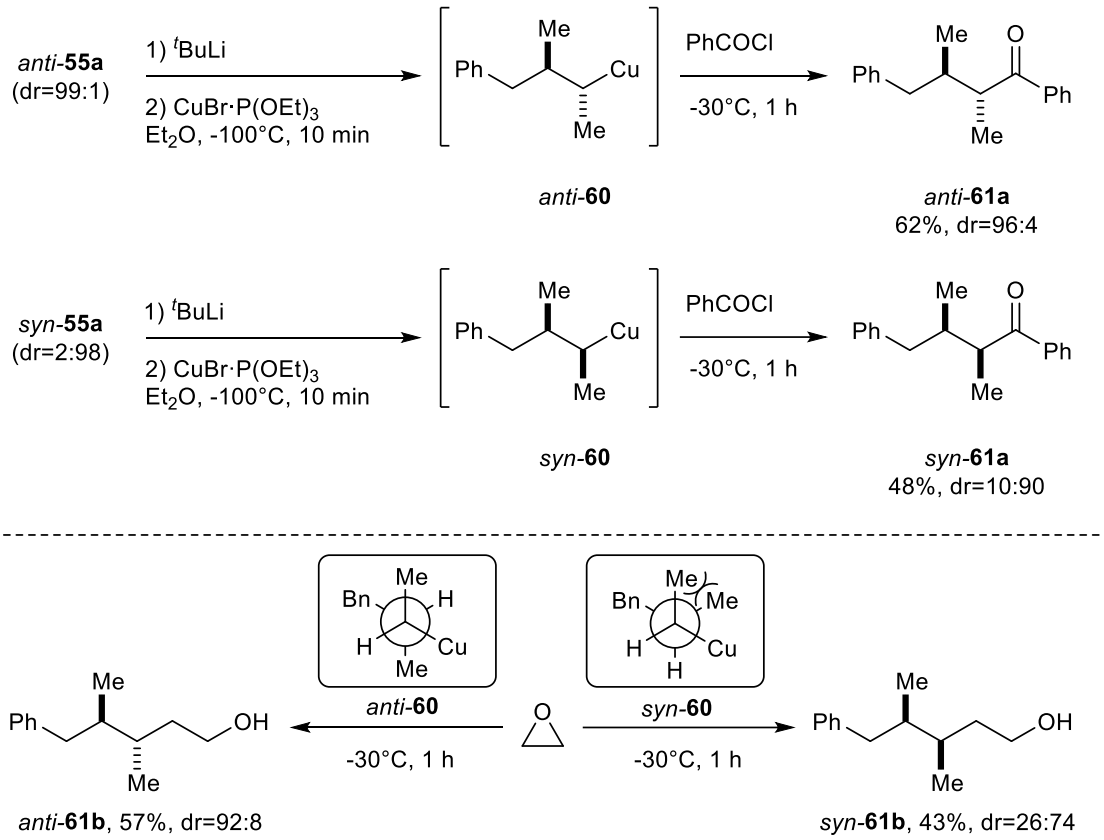
anti-**56a** or *syn*-**56a** | *anti*-**55a** or *syn*-**55a** | *anti*-**59**(**57a**) or *syn*-**59**(**57a**)

Entry	Li-reagent[a]	E^+	Product	Yield, dr[b]
1	*anti*-**55a** (99:1)	DMF	 *anti*-**59b**	60%, 95:5
2	*syn*-**55a** (1:99)	DMF	 *syn*-**59b**	70%, 7:93
3	*anti*-**55a** (99:1)		 *anti*-**59c**	71%, 97:3
4	*syn*-**55a** (2:98)		 *syn*-**59c**	50%, 8:92
5	*anti*-**55a** (99:1)	$ClCO_2Et$	 *anti*-**57a**	82%, 97:3
6	*syn*-**55a** (5:95)	$ClCO_2Et$	 *syn*-**57a**	75%, 9:91

[a] Diastereomeric ratio of the corresponding iodides (*anti*-**56a** and *syn*-**56a**). [b] The diastereomeric ratio was determined by NMR analysis.

The electrophile scope can be further extended using a transmetalation with the hexane soluble copper complex $CuBr{\cdot}P(OEt)_3$,[95–97] which was found to be the best transmetalating

agent according to previous results reported by Knochel and co-workers.[78] The secondary alkylcopper reagent (*anti*-**60**), generated by a transmetalation of the corresponding *anti*-**55a** alkyllithium with a solution of $CuBr{\cdot}P(OEt)_3$ in ether (1 M) at -100°C in 10 min, reacted with PhCOCl (-30 °C, 1 h) to provide the *anti*-ketone (*anti*-**61a**) in 62% yield and dr=96:4. Similarly, the *syn*-iodide (*syn*-**55a**, dr=2:98) undergoes a smooth I/Li-exchange and after transmetalation with $CuBr{\cdot}P(OEt)_3$ is leading to the corresponding copper reagent (*syn*-**60**). Benzoylation of *syn*-**60** affords the *syn*-ketone (*syn*-**61a**) in 48% and dr=10:90, indicating a slightly decreased configurational stability of alkylcopper *syn*-**60** compared to the alkylcopper *anti*-**60**. Interestingly, the retentive transmetalation to copper allows also to perform the opening of ethylene oxide[98] with *anti*- and *syn*-**60** alkylcoppers (Scheme 26). In the case of the less sterically hindered copper reagent (*anti*-**60**), a satisfying retention is observed in the formation of the alcohol *anti*-**61b** (dr=92:8, 57% yield). However, in the case of the more sterically congested *syn*-**61b** (see the Newman's projections), an erosion of the diastereoselectivity was observed and the desired alcohol *syn*-**61b** was obtained in 43% yield and a moderate dr of 26:74. This lower diastereoselectivity can be explained by the somewhat lower reactivity of ethylene oxide, leading to a competitive configurational isomerization of *syn*-**60** to *anti*-**60** (Scheme 26).



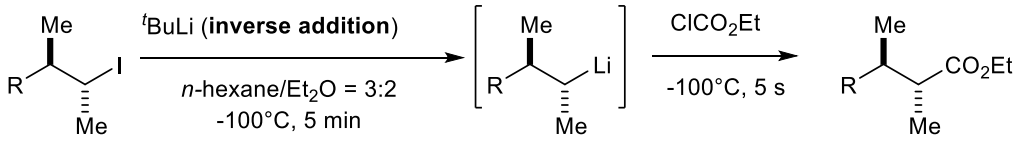
Scheme 26. Stereoselective formation of alkylcopper reagents *anti*-**60** and *syn*-**60** from the alkyl iodides *anti*-**56a** and *syn*-**56b** via I/Li-exchange, transmetalation with $CuBr{\cdot}P(OEt)_3$ and its subsequent reactions with electrophiles.

Substrate scope

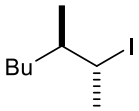
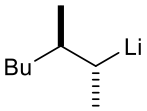
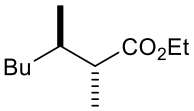
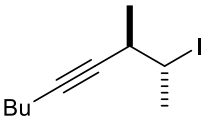
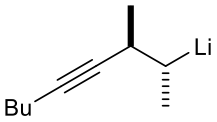
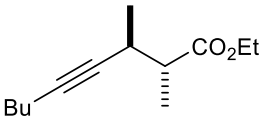
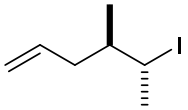
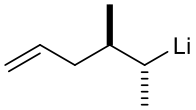
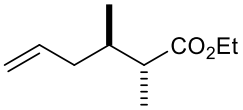
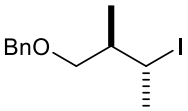
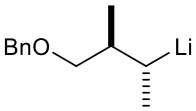
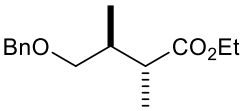
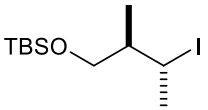
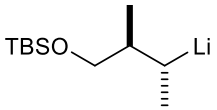
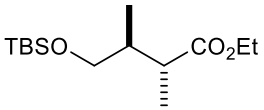
A range of both *anti*- and *syn*-2,3-dimethyl substituted carboxylates of type **57** was prepared starting from readily available alkyl iodides of type **56**. Thus, the *anti*-alkyllithium (**55b**), prepared from the corresponding alkyl iodide (*anti*-**56b**, d.r.=99:1), was treated at -100°C under standard conditions with $ClCO_2Et$ leading to the *anti*-ethyl 2,3-dimethyl carboxylate (*anti*-**57b**) in 86% yield and dr=97:3 (entry 1 of Table 2). Similarly, the *syn*-alkyl iodide (*syn*-**56b**, dr=1:99) was converted by this sequence to the *syn*-2,3-dimethylcarboxylate (*syn*-**57b**) in 63% yield and dr=5:95 (entry 6 of Table 2). Several additional functionalities such as a triple bond, a double bond are perfectly tolerated as well as a protected hydroxyl function. For example, the *anti*-alkyl iodide (*anti*-**56c**, dr=99:1) bearing a triple carbon-carbon bond in γ-position was converted to the corresponding *anti*-ethyl 2,3-dimethylcarboxylic ester (*anti*-**57c**) in 72% yield and dr=97:3 (entry 2 of Table 2). The other diastereomer (*syn*-**57c**) was obtained from the *syn*-alkyl iodide (*syn*-**56c**, dr=1:99) under the same conditions in 61% yield and d.r.=1:99 (entry 7 of Table 2). The treatment of *anti*-alkyl iodide (*anti*-**56d**, dr=97:3) containing a remote double bond with ^{t}BuLi under standard conditions afforded the *anti*-alkyllithium **55d**

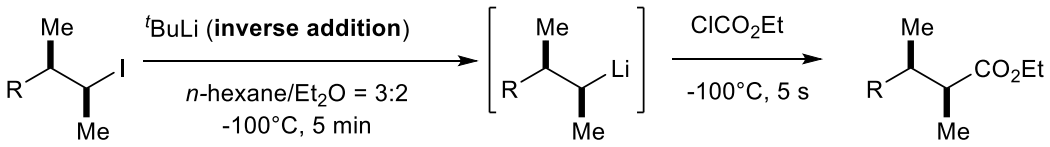
which then reacted with $ClCO_2Et$ to provide the *anti*-carboxylic derivative (*anti*-**57d**) in 64% yield and dr=96:4 (entry 3 of Table 2). A lower retention of configuration was observed in the preparation of the corresponding *syn*-carboxylate **57d** from the *syn*-alkyl iodide (*syn*-**56d**, dr=5:95). Thus, the ester (*syn*-**57d**) was isolated in 69% yield with dr=9:91 (entry 8 of Table 2). The *anti*- and *syn*-benzyloxy protected alkyl iodides (*anti*-**56e**, dr=96:4; and *syn*-**56e**, dr=5:95) were converted to the corresponding *anti*- and *syn*-carboxylic esters (*anti*-**57e** and *syn*-**57e**) in the same manner in 60-77% yield (dr=91:9 and dr=10:90; entries 4 and 9 of Table 2, respectively). The *anti*- and *syn*- alkyl iodides bearing an OTBS-group (TBS = *tert*-butyldimethylsilyl) at γ-position (*anti*-**56f**, dr=97:3; and *syn*-**56f**, dr=5:95) were treated under the same conditions to afford *anti*-**55f** and *syn*-**55f** which reacted with $ClCO_2Et$ leading to the ethyl-2,3-dimethylcarboxylic esters *anti*-**57f** in 72% yield and dr= 94:6 and *syn*-**57f** in 59% yield and dr=8:92 (entries 5 and 10 of Table 2). Thus, in all cases the retention of the configuration is higher than 94%. The best results are obtained from *anti*-lithium reagents, whereas the *syn*-alkyllithiums which are more sterically congested (Scheme 23) and less configurationally stable are leading to somewhat lower diastereoselectivities (entries 6, 8 and 10 of Table 2). Interestingly, in the case of lithium reagents **55e** and **55f**, the thermodynamic equilibration experiments (-50 °C, 30 min, $ClCO_2Et$ was used as an electrophile) showed a diastereomeric ratio of the *anti*-**55e** to *syn*-**55e** of 34:66 compared to 91:9 (kinetic quenching) and a diastereomeric ratio of the *anti*-**55f** to *syn*-**55f** of 15:85 compared to 94:6 (kinetic quenching), accordingly. As was already mentioned in the Introduction, the coordination of Li to OTBS substituted species at position 3 could lead to exclusive formation of only one diastereomer (Scheme 14).[74] Therefore, the observed diastereoselectivity in case of lithium reagents **55e** and **55f** in the thermodynamic conditions could be also explained by a similar intramolecular coordination of lithium to oxygen, where the methyl groups interact the least.

Table 2. Diastereoselective synthesis of *anti-* and *syn*-ethyl-2,3-dimethyl carboxylates **57b-f** from the alkyl iodides **56b-f** via I/Li-exchange and following trapping with $ClCO_2Et$ after 5 sec.

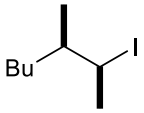
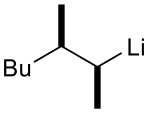
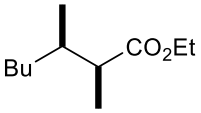
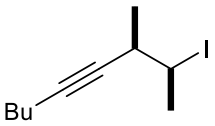
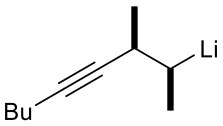
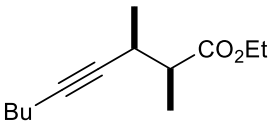
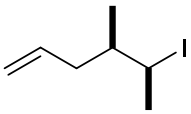
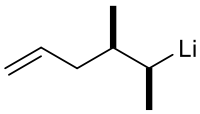
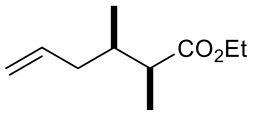
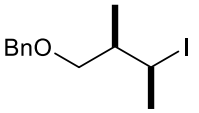
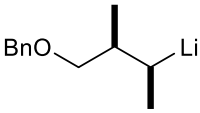
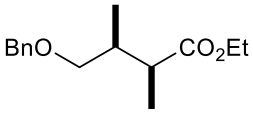
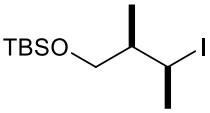
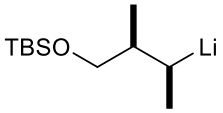
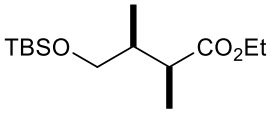


anti-**56** *anti*-**55** *anti*-**57**

Entry	Iodide	Li-reagent	Product[a]
1			
	anti-**56b**, dr=99:1	*anti*-**55b**	*anti*-**57b**, 86%, dr=97:3
2			
	anti-**56c**, dr=99:1	*anti*-**55c**	*anti*-**57c**, 72%, dr=97:3
3			
	anti-**56d**, dr=97:3	*anti*-**55d**	*anti*-**57d**, 64%, dr=96:4
4			
	anti-**56e**, dr=96:4	*anti*-**55e**	*anti*-**57e**, 77%, dr=91:9
5			
	anti-**56f**, dr=96:4	*anti*-**55f**	*anti*-**57f**, 71%, dr=97:3



syn-**56** *syn*-**55** *syn*-**57**

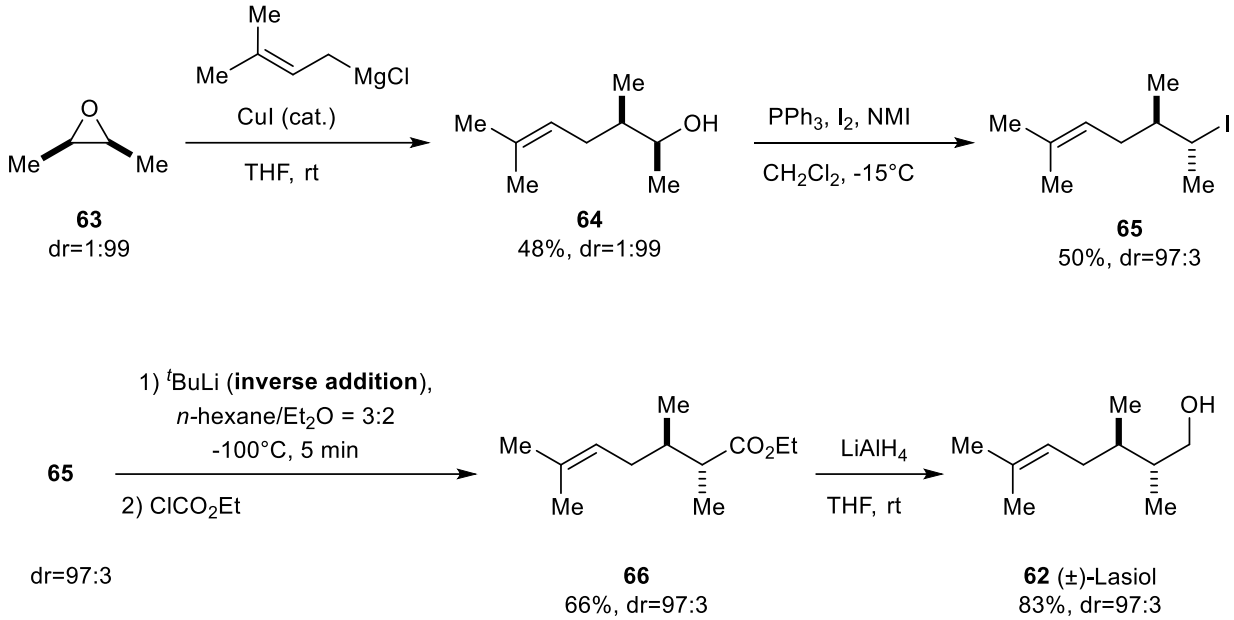
Entry	Iodide	Li-reagent	Product[a]
6			
	syn-**56b**, dr=1:99	*syn*-**55b**	*syn*-**57b**, 63%, dr=5:95
7			
	syn-**56c**, dr=1:99	*syn*-**55c**	*syn*-**57c**, 61%, dr=1:99
8			
	syn-**56d**, dr=5:95	*syn*-**55d**	*syn*-**57d**, 69%, dr=9:91
9			
	syn-**56e**, dr=5:95	*syn*-**55e**	*syn*-**57e**, 60%, dr=10:90
10			
	syn-**56f**, dr=5:95	*syn*-**55f**	*syn*-**57f**, 59%, dr=8:92

[a] The diastereomeric ratio was determined by NMR analysis.

Application

I have also prepared an ant sex pheromone (±)-lasiol[99–101] (alcohol **62**) in 4 steps and 26% overall yield starting from the commercially available *cis*-2,3-epoxybutane **63** (Scheme 27). First, the alcohol **64** was synthesized using the epoxide opening reaction with prenylmagnesium chloride[102] in the presence of catalytic amounts of CuI (10 mol.%)[92] in

98 % yield and dr=99:1. The obtained alcohol **64** was iodinated with complete inversion of the configuration under the Appel conditions,[90] providing the secondary alkyl iodide **65** in 50% yield with a slight loss of diastereoselectivity (dr=97:3). The alkyl iodide **65** was converted to the corresponding lithium reagent using retentive I/Li-exchange and its subsequent trapping with $ClCO_2Et$ afforded the ester **66** in 66% yield and dr=97:3. The ester **66** was further converted to (±)-lasiol (**62**) using $LiAlH_4$ reduction (83% yield and dr=97:3).

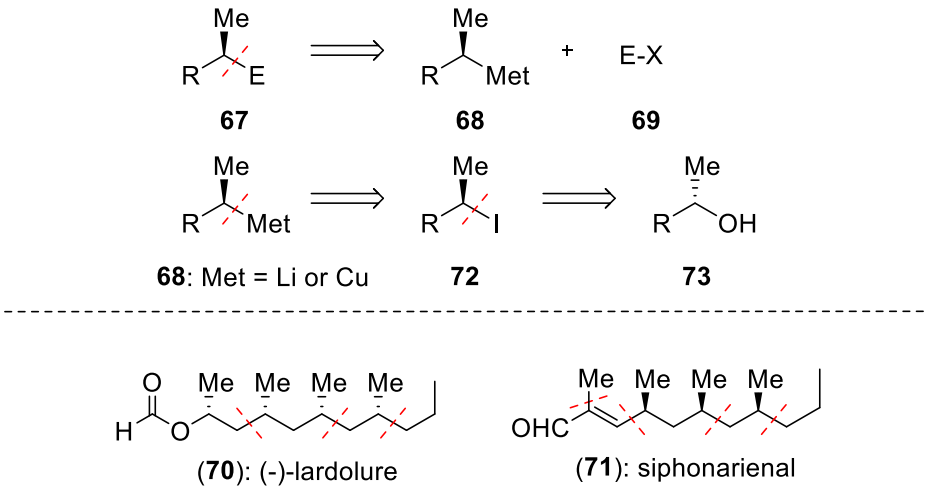


Scheme 27. Diastereoselective synthesis of (±)-lasiol (**62**) from *cis*-2,3-epoxybutane (**63**).

In summary, a retentive I/Li-exchange reaction of α-chiral secondary iodides leading to chiral secondary alkyllithium building blocks was developed. These chiral lithium reagents were used to prepare various 2,3-dimethyl carboxylic ester derivatives often encountered in natural product targets with high diastereoselectivity. The method was extended to the stereoselective preparation of carboxylic derivatives bearing stereotriads and the sex ant pheromone (±)-lasiol.

Preparation of Optically Enriched Secondary Alkyllithium and Alkylcopper Reagents. Synthesis of (-)-Lardolure and Siphonarienal[2]

The preparation of optically enriched acyclic molecules bearing several chiral centers is an important task in organic synthesis. Often chiral auxiliaries or catalytic asymmetric reactions have been used to construct such molecules.[8,103,104] Most retrosynthetic analyses for the elaboration of chiral targets of type **67** involve standard organic reactions such as aldol reactions, Michael additions or related transformations. An alternative retrosynthetic analysis can be envisioned, involving the cleavage of a C-C bond at the chiral center. This disconnection requires the reaction of an optically enriched organometallic reagent **68** (Met = Li or Cu) with an electrophile E-X (**69**). Such a reaction will be stereoselective, if the organometallic species of type **68** are configurationally stable under the reaction conditions. (Scheme 28).



Scheme 28. Retrosynthetic analysis of target molecules **70** and **71**.

In this chapter the preparation of optically enriched (>90% *ee*) unstabilized secondary alkyllithiums and alkylcoppers (**68**) will be discussed. Also their high versatility for the preparation of a range of polyfunctional optically enriched organic molecules will be shown.

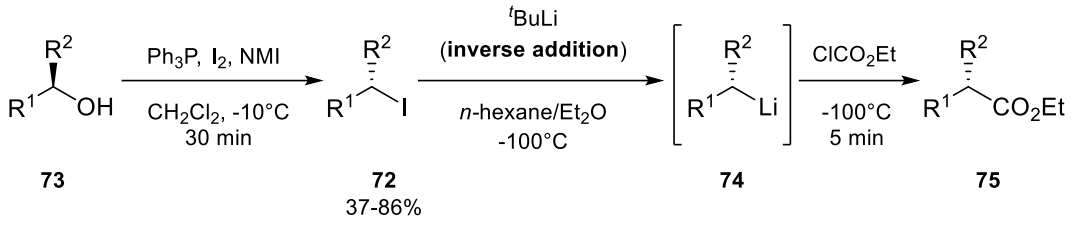
[2] This project was performed in a cooperation with J. Skotnitzki and K. Moriya.

Using this method, I have prepared in an iterative fashion of two related natural products (-)-lardolure (**70**)[3,105–109] and siphonarienal (**71**).[110–115]

Synthesis of the secondary alkyl metallics and their reactivity

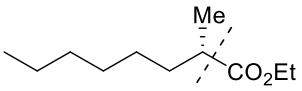
The secondary alkyl iodides of type **72** could be synthesized from commercially available or accessible by other methods chiral alcohols (**73**) via Appel iodination[90] with the inversion of the configuration, similar to iodides **56** (see previous chapter). Thus, a range of readily prepared optically enriched alcohols (**73a**-**g**, 95-99% *ee*) were converted to the corresponding iodides (**73a**-**g**) with complete inversion of configuration. A retentive I/Li-exchange provided configurationally stable secondary alkyllithiums (**74a**-**g**) (-100 °C, 2 min). These chiral secondary alkyllithiums were trapped with $ClCO_2Et$ affording a variety of highly optically enriched carboxylic esters of type **75** in 90-99% *ee* and 54-62% yield (Table 3). The enantiomeric purity of the starting alcohols (**73**), most alkyl iodides (**72**) and of the chiral esters (**75**) were determined by chiral HPLC- and GC-analysis.

Table 3. Enantioselective synthesis of esters **75a-h** starting from optically enriched alcohols (**73a-h**) via iodination, I/Li-exchange and quench with $ClCO_2Et$.

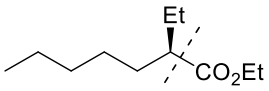


73 **72** 37-86% **74** **75**

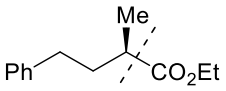
Products of type **9**[a]



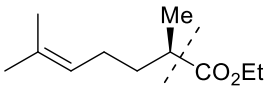
S-**75a**
59% yield, 90.2% *ee*[b]
(from 96.0% *ee* of *R*-**73a**)



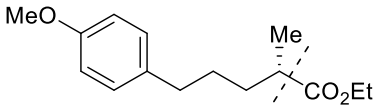
R-**75b**
54% yield, 93.0% *ee*[b]
(from 95.5% *ee* of *S*-**73b**)



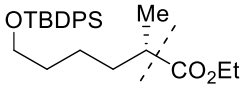
R-**75c**
58% yield, 90.2% *ee*[b]
(from 97.8% *ee* of *S*-**73c**)



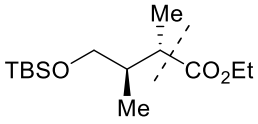
R-**75d**
56% yield, 97.3% *ee*[b]
(from 97.3% *ee* of *S*-**73d**)



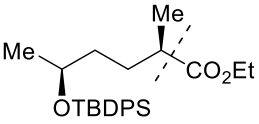
S-**75e**
61% yield, 92.0% *ee*[b]
(from >99% *ee* of *R*-**73e**)



S-**75f**
62% yield, 93.8% *ee*[b]
(from >99% *ee* of *R*-**73f**)



2S,3R-**75g**
70% yield, dr=95:5[c]
(from >99% *ee* and
dr=98:2 of *2R,3S*-**73g**)



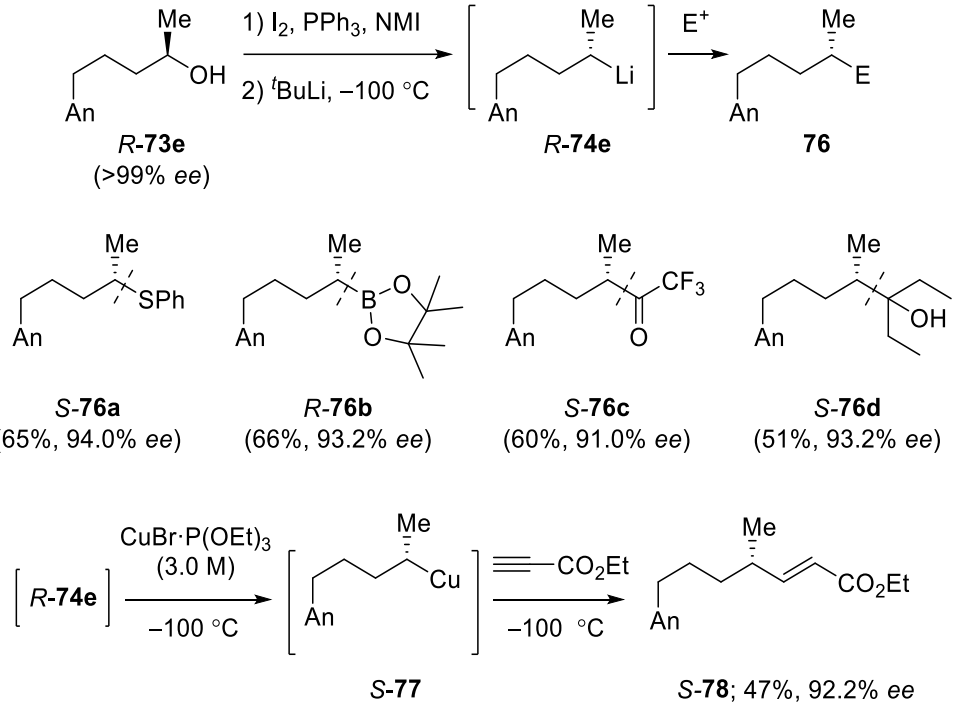
2R,5S-**75h**
56% yield, dr=99:1[c]
(from >99% *ee* and
dr=98:2 of *2S,5S*-**73h**)

[a] Isolated yields. [b] The enantiomeric excess (*ee*) was determined by chiral HPLC- and GC- analysis. [c] The diastereomeric ratio was determined by NMR-analysis. NMI = 1-methylimidazole.

Besides carboxylation with $ClCO_2Et$, other electrophiles react with retention of configuration with chiral secondary alkyllithiums of type **74**, producing a variety of synthetically useful chiral molecules of type **76** (Scheme 29). Thus, the alkyl iodide (*S*-**72e**) was obtained from the alcohol (*R*-**73e**, >99% *ee*) with complete inversion and was further converted to the enantiomerically enriched secondary alkyllithium (*R*-**74e**) using an I/Li-exchange. Thiophenylation of *R*-**74e** with Ph_2S_2 (-100 °C, 5 min) led to the thioether *S*-**76a** in 65% yield and 94.0% *ee*. Borylation of *R*-**74e** with MeOBpin provided the boronic ester *R*-**76b** in 66% yield and 93.2% *ee*. Acylation with Weinreb-amide $CF_3CON(OMe)Me$ furnished the optically enriched trifluoromethyl ketone *S*-**76c** in 60% yield and 91% *ee*. Addition of diethyl ketone to *R*-**74e** gave the chiral tertiary alcohol *S*-**76d** in 51% yield and 93.2% *ee*.

The range of electrophiles can be further extended by performing a transmetalation of the chiral alkyllithium *R*-**74e** to the corresponding copper reagent (*S*-**77**). After considerable

optimization, we have found that the addition of a 3 M ether solution of $CuBr \cdot P(OEt)_3$ to the alkyllithium reagent *R*-**74e** at -100 °C within 3 min provides the corresponding secondary alkylcopper *S*-**77** with >97% retention of configuration. Thus, this alkylcopper *S*-**77** undergoes a smooth addition to ethyl propiolate (-100 to -80 °C, 30 min) leading after acidic quench to the chiral ethyl acrylate (*S*-**78**) in 47% yield and 92.2% *ee*.



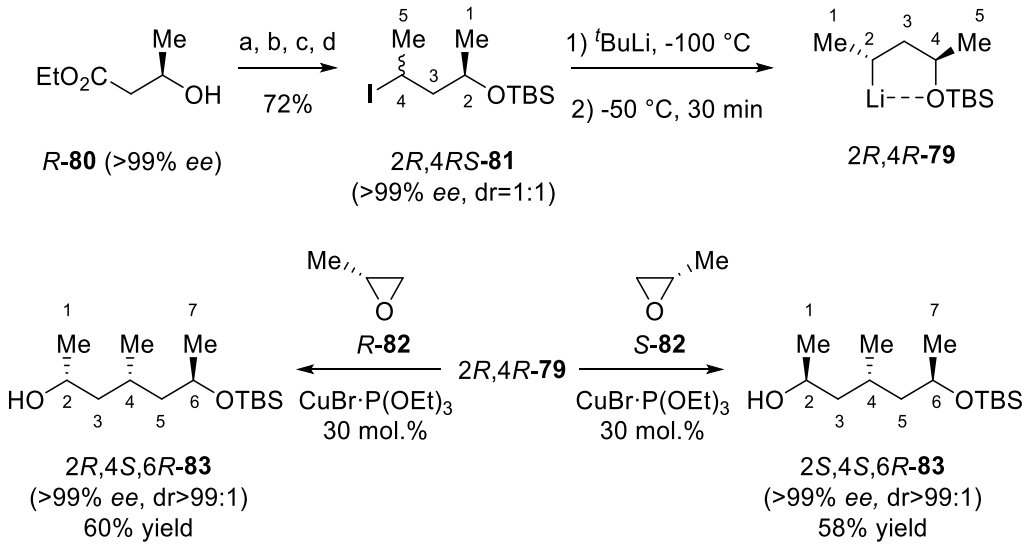
Scheme 29. Stereoselective trapping of alkyllithium *R*-**74e** with various electrophiles and transmetalation to copper reagent *S*-**77** with a subsequent carbocupration with ethyl propiolate. An=4-$MeOC_6H_4$.

Detailed study of the stability of *R*-**74e** and *S*-**77** depending on the temperatures showed, that *R*-**74e** racemizes rapidly at -80 °C and higher temperatures, whereas *S*-**77** keeps the configuration even at -40 °C (details are in the Experimental part).

Application towards natural product synthesis

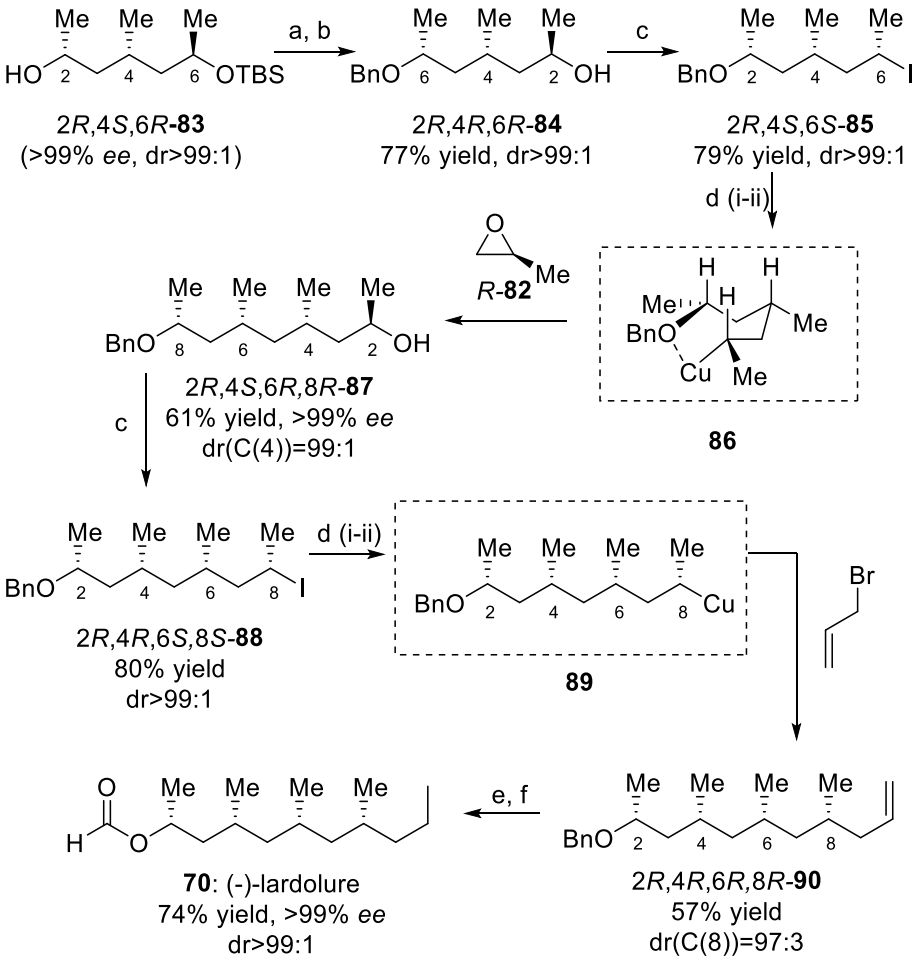
After the examination of the scope of the reactions of chiral organometallics of type **68**, the methodology was applied to the total synthesis of two complex molecules (-)-lardolure (**70**) and siphonarienal (**71**). In all shown cases, the configuration of alkyllithiums and coppers directly transferred from the corresponding asymmetric alkyl iodides. However, there is an important case concerning secondary alkyl iodides bearing a 2-OTBS substituent. In this case, the configuration of the carbon center bearing lithium can be set by equilibration producing only one diastereomer.[74] This has been used to prepare enantiomerically enriched secondary alkyllithium 2*R*,4*R*-**79** starting from commercially available *R*-**80** (Scheme 30). By a standard

sequence of functional group transformations, we have converted *R*-**80** (>99% *ee*) to an epimeric mixture of the secondary alkyl iodide 2*R*,4*RS*-**81** (dr=1:1; >99% *ee*). As expected, an I/Li-exchange of 2*R*,4*RS*-**81** with ^{t}BuLi at -100 °C, followed by an equilibration of C(4) (-50 °C, 30 min), produced exclusively 2*R*,4*R*-**79** alkyllithium. This key alkyl lithium intermediate (2*R*,4*R*-**79**) opens diastereoselectively (*R*)- or (*S*)-propylene oxide (*R*-**82** or *S*-**82**) in the presence of 30% CuBr·P(OEt)$_3$ (-50 °C, 2 d). These reaction conditions were carefully optimized and were found superior to a stoichiometric transmetalation to copper. The stoichiometric transmetalation to the corresponding copper reagent led to epimerization at C(2), providing the products **83** as 80:20 mixture of diastereomers. The use of catalytic amounts of copper was possible due to the exceptional stability of the chelate-stabilized 2*R*,4*R*-**79**. Remarkably, these catalytic reaction conditions allowed to scale-up the epoxide opening to a 10 mmol-scale. Thus, the treatment of 2*R*,4*R*-**79** with *R*-**82** or *S*-**82** produces respectively the corresponding diols 2*R*,4*S*,6*R*-**83** and 2*S*,4*S*,6*R*-**83** in >99% *ee* as only one diastereomer. Important to note, that crude reaction mixture indicates a slight epimerization at C(2) (crude dr=97:3). After chromatographic purification, the dr at C(2) was >99:1. The two enantiomerically pure alcohols 2*R*,4*S*,6*R*-**83** and 2*S*,4*S*,6*R*-**83** were used to prepare two natural products (-)-lardolure (**70**) and siphonarienal (**71**) using an iterative approach. The *ee* and absolute configuration of alcohols **83** was determined using Mosher's ester analysis.[116]



Scheme 30. Towards the synthesis of (-)-lardolure (**70**) and siphonarienal (**71**). Stereoconvergent preparation of the chiral diol derivatives **83**. a) TBSCl, imidazole, CH_2Cl_2, 25 °C, 20 h, 99% yield; b) diisobutylaluminum hydride, toluene, -78 °C, 1 h, 98% yield; c) MeLi, THF, -78 °C, 20 min, 89% yield; d) PPh_3, I_2, NMI, CH_2Cl_2, -10 °C, 1 h, 84% yield.

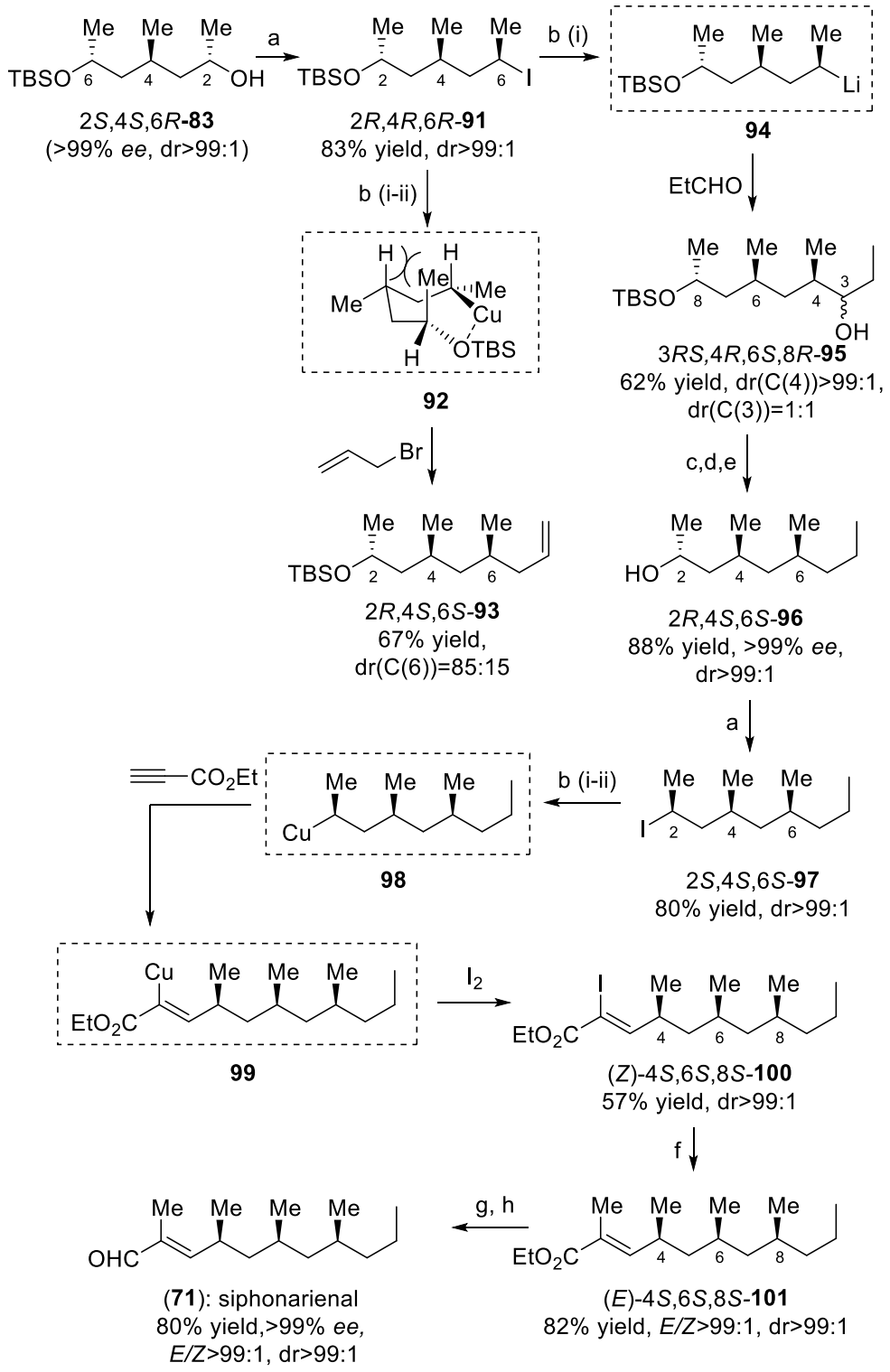
Thus, the alcohol 2*R*,4*S,*6*R*-**83** was converted by two functional group interconversions to the alcohol 2*R*,4*R,*6*R*-**84** (77% yield, dr>99:1), which by Appel reaction is furnishing with complete inversion the secondary alkyl iodide 2*R*,4*S,*6*S*-**85**. Applying the I/Li - interconversion sequence to 2*R*,4*S,*6*S*-**85** followed by a transmetalation to the corresponding chiral alkylcopper reagent **86** and subsequent opening of the epoxide (*R*-**82**) provided the secondary alcohol 2*R*,4*S,*6*R,*8*R*-**87** with complete retention of chirality at C(4) and in 61% yield. Repeating the same sequence (eg. iodination with inversion providing 2*R*,4*R,*6*S,*8*S*-**88** and I/Li/Cu – exchange gives an intermediate organocopper **89** which after allylation furnishes the benzylic ether 2*R*,4*R,*6*R,*8*R*-**90** (57% yield, dr(C(8))=97:3). After Pd-catalyzed hydrogenation[111] and formylation[105,107–109], the pheromone (-)-lardolure (**70**) was obtained in 74% yield (dr(C(8))=99:1, >99% *ee*; Scheme 31). The comparison of obtained analytical data with the reported ones[3,105–109] proves the stereochemical identity.



Scheme 31. Total synthesis of **70** (-)-lardolure. a) NaH, benzyl bromide, THF, reflux, 48 h; b) TBAF·3H_2O, THF, reflux, 24 h; c) PPh_3, I_2, NMI, CH_2Cl_2, -10 °C, 1 h; d) (i): ^{t}BuLi, inverse addition, ether:hexane, -100 °C, 1 min; (ii): CuBr·$P(OEt)_3$, ether:hexane, -100 °C, 1 min; electrophile, -100 °C to -80 °C, 1 h; e) Pd/C, H_2, EtOAc, 25 °C, 2 h; f) HCOOH, 65 °C, 1 h. THF = tetrahydrofuran; TBAF = tetrabutylammonium fluoride.

Using the epimeric alcohol 2*S*,4*S,*6*R*-**83** (Scheme 32), we have prepared in a related iterative manner the natural product siphonarienal (**71**) isolated from a mollusc.[110–115] Thus, 2*S*,4*S,*6*R*-**83** was iodinated to the inverted secondary iodide 2*S*,4*S,*6*S*-**91** (83% yield, dr(C(2)>99:1). The standard I/Li-exchange followed by a transmetalation with CuBr·$P(OEt)_3$ provided a copper intermediate **92** which, unfortunately, was configurationally labile under the allylation conditions providing a 85:15 mixture of diastereomers at C(6) of **93**. This may be due to the axial-methyl group at C(6) which hampers an intramolecular stabilization by chelation at the OTBS-group and facilitates epimerization of C(6). Thus, an envisioned alternative introduction of the propyl unit using the reaction of corresponding Li-intermediate (**94**) with propionaldehyde was performed. This addition provided the alcohol *3RS*,4*R,*6*S*,8*R*-**95** as 1:1 mixture of diastereomers at C(3), but as a single diastereomer at C(4) in 62% yield. After mesylation, reduction with $LiAlH_4$ and TBS-deprotection, the alcohol 2*R*,4*S,*6*S*-**96** was

obtained in 88% yield over 3 steps as a single diastereomer and enantiomer (dr>99:1, >99% *ee*). This alcohol (2*R*,4*S*,6*S*-**96**) was further converted to the corresponding iodide (2*S*,4*S*,6*S*-**97**) with complete inversion of C(2) (dr>99:1). After retentive I/Li-exchange and subsequent copper transmetalation, the alkylcopper reagent **98** added to ethyl propiolate (-100 °C, 3 min) to give the (*Z*)-alkenylcopper intermediate **99**. The direct methylation with various electrophiles like MeI, $(MeO)_2SO_2$ and MeOTf provided the compound **101** in the best only in 28% yield. Therefore, the copper reagent **99** was iodinated with I_2 to provide (*Z*)-4*S*,6*S*,8*S*-**100** in 57% yield. This iodide slightly isomerizes over the time. Negishi cross-coupling of iodide (*Z*)-4*S*,6*S*,8*S*-**100** with $MeZnCl{\cdot}MgCl_2$ led to the unsaturated ester (*E*)-4*S*,6*S*,8*S*-**101** in 82% yield with retention of configuration of the double bond. After reduction of the ester group of (*E*)-4*S*,6*S*,8*S*-**101** and subsequent oxidation with MnO_2, the natural product siphonarienal (**71**) was obtained in 80% yield over the last two steps. The comparison of obtained analytical data with the reported ones[110–115] proves the stereochemical identity. The allylic aldehyde siphonarienal (**71**) rapidly oxidizes to the corresponding acid under air.



Scheme 32. Total synthesis of **71** siphonarienal. a) PPh_3, I_2, NMI, CH_2Cl_2, -10 °C, 1 h; b) (i): ^{t}BuLi, inverse addition, ether:hexane, -100 °C, 1 min; (ii): CuBr·P(OEt)$_3$, ether:hexane, -100 °C, 1 min; electrophile, -100 °C to -80 °C, 1 h; c) mesyl chloride, Et_3N, CH_2Cl_2, 0 °C, 2 h; d) $LiAlH_4$, ether, rt, 12 h; e) TBAF·3H_2O, THF, rt, 12 h; f) MeZnCl·$MgCl_2$, $Pd(OAc)_2$, S-Phos, THF, 0 °C, 2 h; g) diisobutylaluminum hydride, toluene, -78 °C, 1 h; h) MnO_2, hexanes, rt, 3 h.

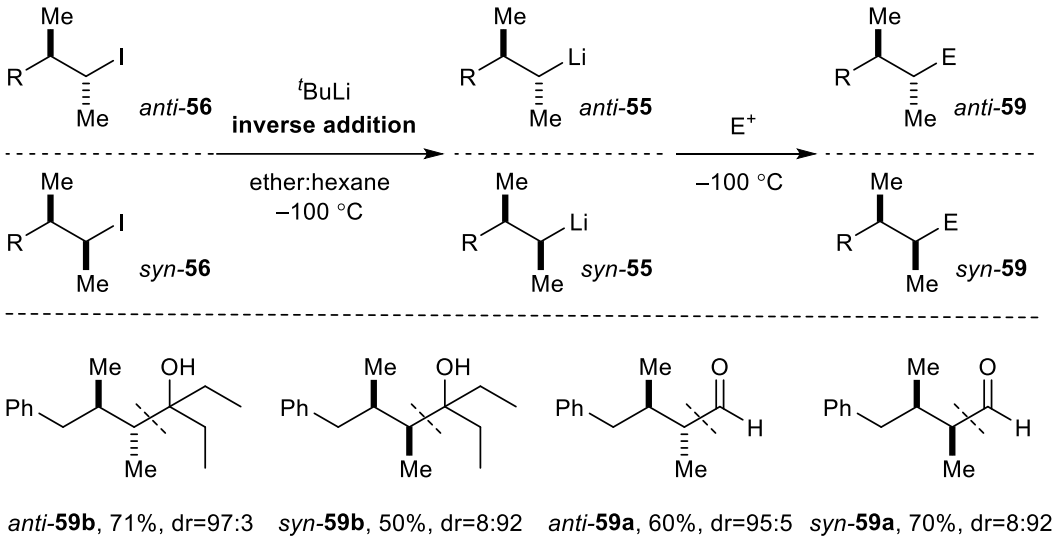
In summary, various highly optically enriched secondary alcohols were converted via inverted secondary alkyl iodides, to secondary alkyl-lithium and -copper intermediates that reacted with various electrophiles with high retention of configuration. This method has been used to prepare two related natural products (-)-lardolure (**70**) and siphonarienal (**71**) in >99% *ee* with a complete control of the relative stereochemistry of all stereocenters.

Summary

Summary

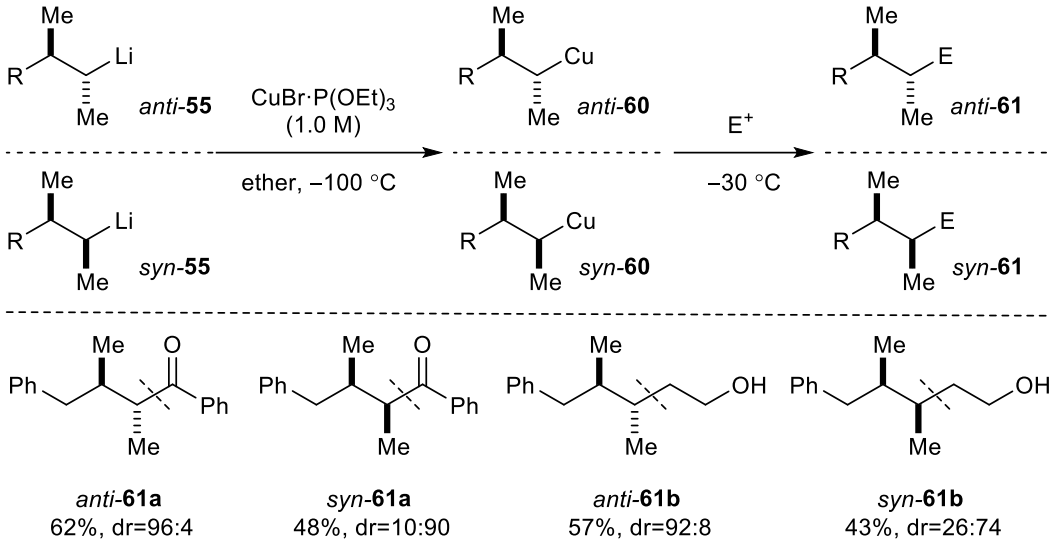
My research was focused on the development of new chiral organometallic reagents, particularly organolithiums and coppers, and their application to total synthesis of various natural products.

First, highly stereoselective preparation of α-chiral alkyllithiums of type **55** starting from the corresponding iodides (**56**) was established as well as their application to the stereoselective synthesis (Scheme 33). Thus, the inverse addition of α-chiral secondary alkyl iodides to ^{t}BuLi solution at -100 °C leads to the corresponding secondary alkyllithiums with high retention of configuration. The following quenching with various electrophiles provides the desired products (**59**) with high retention of configuration in good to excellent yields (Scheme 33).



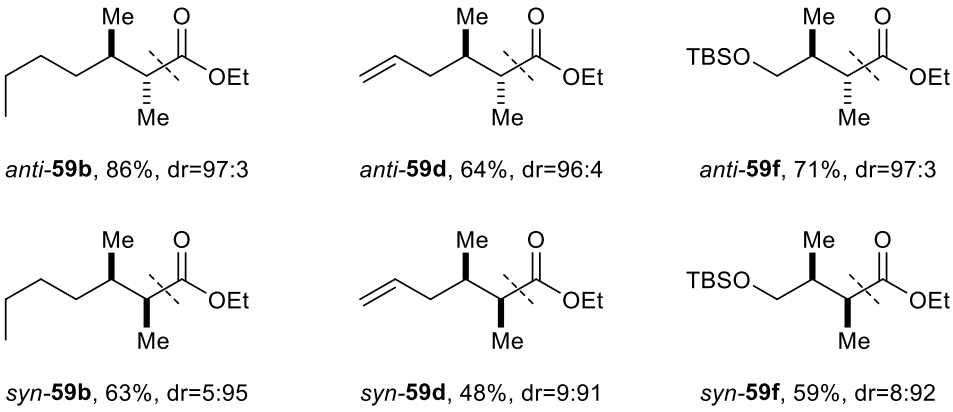
Scheme 33. Diastereoselective generation of α-chiral *anti*- and *syn*-secondary alkyllithiums (**55**) from the secondary alkyl iodides (**56**) and subsequent reaction with electrophile (E^{+}). Selected examples are presented.

Furthermore, a transmetalation with a 1 M ether solution $CuBr{\cdot}P(OEt)_3$ also allows to extend the synthetic utility of these reagents. The resulting copper reagent (**60**) stereoselectively reacts with acid chlorides and ethylene oxide, providing the corresponding products (**61**) (Scheme 34). In a case of agent *syn*-**60** considerable loss of diastereoselectivity was observed.



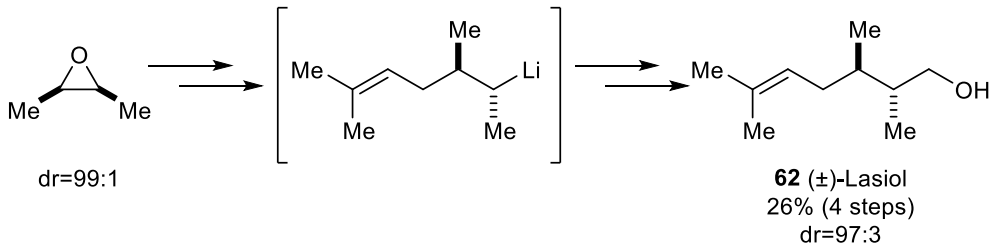
Scheme 34. Diastereoselective generation of α-chiral *anti*- and *syn*-secondary alkylcoppers (**4**) from the corresponding alkyllithiums (**1**) and subsequent reaction with electrophile (E^+). Selected examples are presented.

It was also shown that this process has a broad substrates scope. The quenching of the alkyllithiums with $ClCO_2Et$ furnishes stereoselectively a variety of *syn*- and *anti*-ethyl-2,3-dimethyl ester carboxylates (**59**) (dr>94%, Scheme 35).



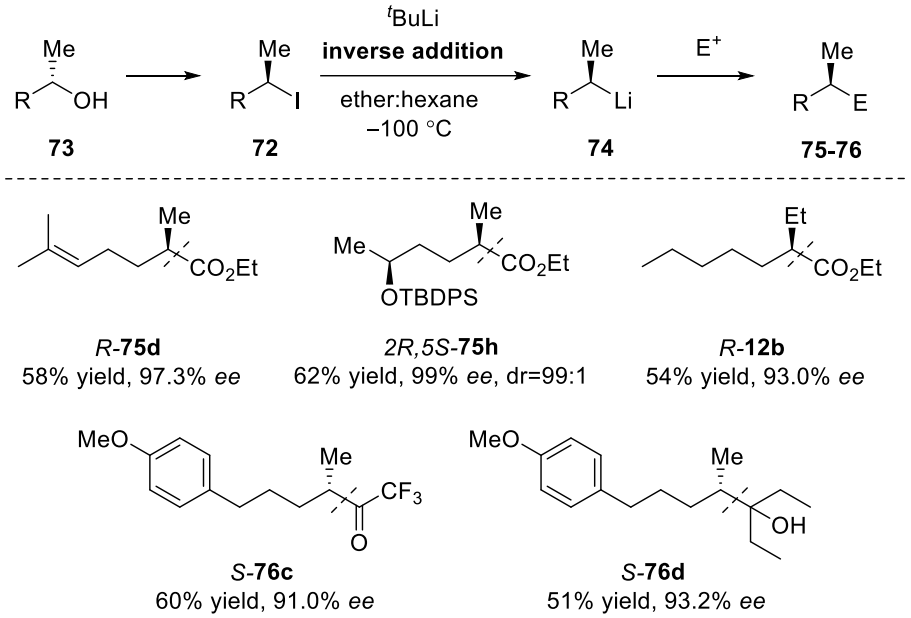
Scheme 35. Diastereoselective synthesis of *anti*- and *syn*-ethyl-2,3-dimethyl carboxylates (**59**). Selected examples are presented.

This method has been applied to the synthesis of the ant pheromone (±)-lasiol (**62**) in 26% overall yield (four steps) with dr=97:3 starting from commercially available *cis*-2,3-epoxybutane (Scheme 36).



Scheme 36. Diastereoselective synthesis of (±)-lasiol (**62**) from *cis*-2,3-epoxy-butane.

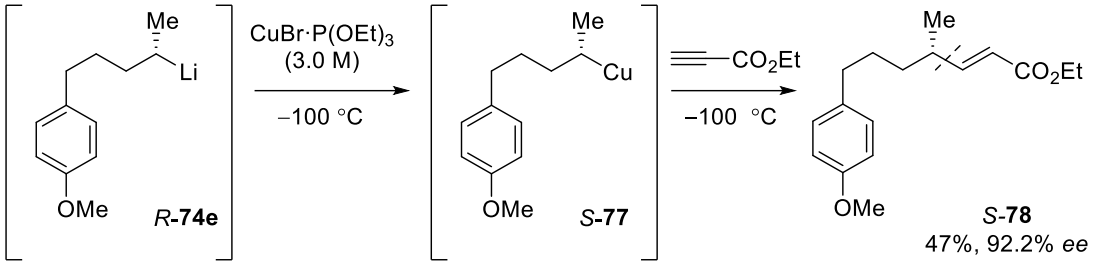
In the second part, we have reported a stereoselective preparation of chiral secondary alkyllithiums (**74**) and alkylcoppers (**77**) (>90% *ee*), starting from commercially available secondary alcohols (**73**) via iodination (Appel reaction, **72**) and subsequent I/Li-exchange .The organolithium reagents of type **72** were obtained in a similar way as α-chiral lithiums, employing an inverse addition of ^{t}BuLi at -100 °C (Scheme 37). Retentive quenching of these chiral alkyllithiums with various electrophiles, like Weinreb amide, $ClCO_2Et$, etc. provided polyfunctional chiral molecules (**75**-**76**).



Scheme 37. Enantioselective synthesis of various chiral compounds (**75-76**) via a retentive I/Li-exchange. Selected examples are presented.

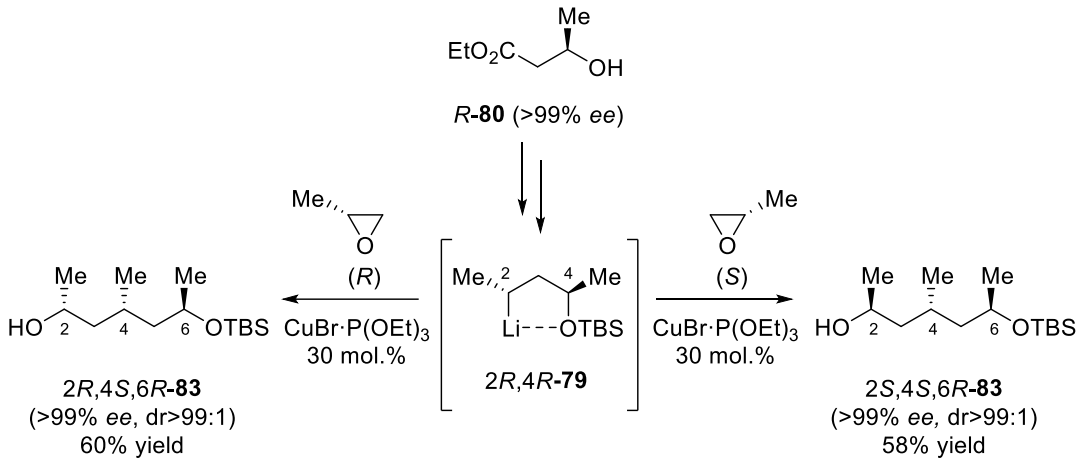
The electrophile scope can be extended performing a transmetalation of the alkyllithium reagent to the corresponding organocopper reagent (**77**) (Scheme 38). It was found that the best stereoselectivity can be achieved by the usage of a 3 M ether solution of $CuBr{\cdot}P(OEt)_3$ at -100 °C. The formed alkylcopper *S*-**77** adds to ethyl propiolate providing the chiral ethyl

acrylate (*S*-**78**) in 47% yield and 92.2% *ee*. The formed organocopper reagent (*S*-**77**) is highly configurationally stable even up to -60 °C.



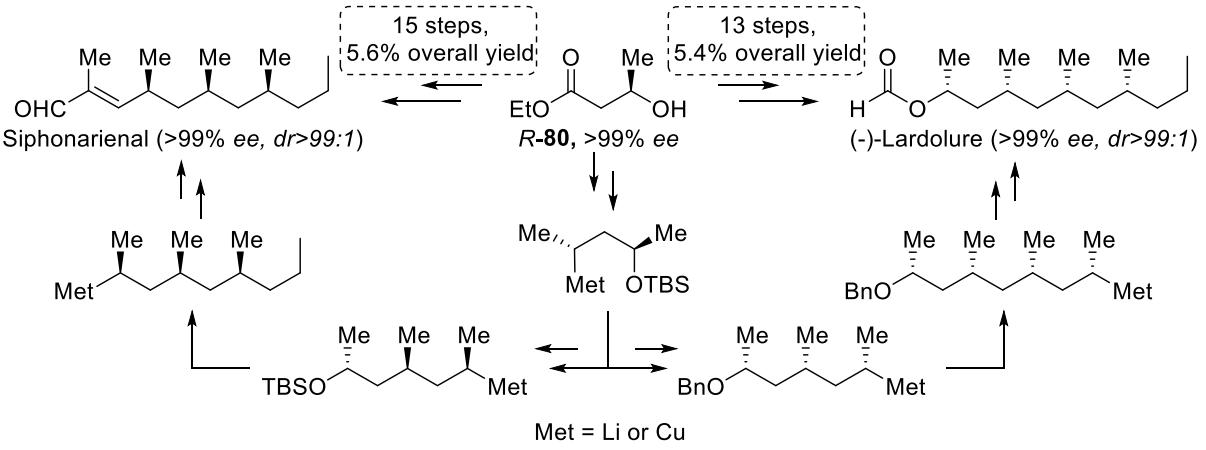
Scheme 38. Enantioselective retentive transmetalation of alkyllithium *R*-**74e** to the corresponding alkylcopper *S*-**77** and subsequent reaction with ethyl propiolate to *S*-**78**.

The ability to generate highly stable alkyllithium **79** allowed to perform epoxide opening reaction in the presence of 30% CuBr·P(OEt)$_3$ on a 10 mmol scale (Scheme 39). The obtained enantiomerically pure alcohols 2*R*,4*S*,6*R*-**83** and 2*S*,4*S*,6*R*-**83** were used to prepare two natural products (-)-lardolure and siphonarienal.



Scheme 39. Stereoconvergent preparation of the chiral diol derivatives **83** via the copper catalyzed epoxide opening.

Finally, (-)-lardolure was obtained in 13 steps and 5.4% overall yield (>99% *ee*, dr>99:1) and siphonarienal was synthesized in 15 steps and 5.6% overall yield (>99% *ee*, dr>99:1) starting from commercially available ethyl (*R*)-3-hydroxybutyrate (**80**) (>99% *ee*). The key intermediates in both synthetic pathways are chiral alkyl organometallics, obtained using the developed methodology (Scheme 40).



Scheme 40. Enantioselective synthesis of (-)-lardolure and siphonarienal from (*R*)-3-hydroxybutyrate (**80**) using chiral organometallics.

Experimental part

General information

Commercially available starting materials were used without further purification unless otherwise stated. The enantiomeric excess (*ee*) of the commercially available compounds was determined in some cases if *ee* was not mentioned. All used liquid electrophiles were distilled before use. All reactions were carried out under Ar atmosphere in flame-dried glassware. Syringes which were used to transfer anhydrous solvents or reagents were purged with Ar prior to use. The concentration of ^{t}BuLi was determined by titration with dry 2-propanol and 1,10-phenanthroline as indicator in THF. THF was refluxed and distilled from sodium benzophenone ketyl under nitrogen. Et_2O was predried over $CaCl_2$ and passed through activated Al_2O_3 (the solvent purification system SPS-400-2 from *Innovative Technologies Inc*.). CH_2Cl_2 was predried over $CaCl_2$ and distilled from CaH_2. 2-Propanol was refluxed and distilled from Mg. *Huber T100* was used for cooling reaction mixtures. Column chromatographical purification was performed using silica gel (SiO_2, 0.040-0.063 mm, 230-400 mesh ASTM) from Merck or alumina (Al_2O_3, 0.063-0.20 mm) from Merck. The spots were visualized by staining of the TLC plate with the permanganate solution ($KMnO_4$·$12MoO_3$ 3.0 g, K_2CO_3 20.0 g, KOH 1.3 g, H_2O 180 mL) followed by heating. PTLC (preparative thin layer chromatography) was performed using SiO_2 pre-coated glass plates (Merck 60, F-254). Yields refer to isolated yields of compounds estimated to be >95% pure as determined by ^{1}H-NMR spectroscopy and capillary gas chromatography analysis. The ratio of diastereomers was determined by ^{1}H NMR or ^{13}C NMR spectroscopy.

NMR spectra were measured on a *Bruker* Avance III HD 400 MHz spectrometer equipped with a CryoProbe™, *Bruker* AXR300, *Varian* VXR400 S, *Bruker* AMX600 or *Bruker* Avance HD 800. Chemical shifts in ppm refer to the solvent residual signal in $CDCl_3$ (δ_H 7.24, δ_C 77.16 ppm) and C_6D_6 (δ_H 7.16, δ_C 128.06 ppm) as internal standard or to external $CFCl_3$ (δ_F 0.0 ppm), respectively. ^{11}B NMR spectra (128 MHz) were obtained by using a JEOL ECX-400 spectrometer and referenced to external BF_3·OEt_2 (δB 0.0 ppm). Abbreviations for signal coupling are as follows: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), h (sextet), hept (heptet) m (multiplet) as well as br (broad).

Enantiomeric excess (*ee*) of the compounds were measured by *Shimazu* HPLC Prominence with *Daicel* Chiralcel or using chiral GC. Optical rotation values were recorded on a

PerkinElmer 241 or *Anton Paar* MCP 200 polarimeter. The specific rotation is calculated as follows:

$$[\alpha]_{\lambda}^{\varphi} = \frac{[\alpha] \cdot 100}{c \cdot d}$$

Thereby, the wavelength λ is reported in nm and the measuring temperature ϕ in °C. *α* represents the recorded optical rotation, *c* the concentration of the analyte in 10 mg/mL and d the length of the cuvette in dm. Thus, the specific rotation is given in 10^{-1}·deg·cm^2·g^{-1}. Usage of the sodium D line (λ = 589 nm) is indicated by D instead of the wavelength in nm. The respective concentration as well as the solvent is reported at the relevant section of the experimental section.

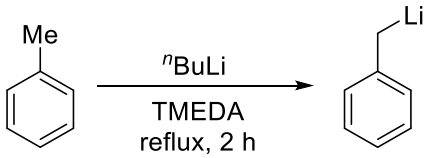
Gas chromatography was performed with machines of *Agilent Technologies* 7890, using a column of type HP 5 *(Agilent* 5% phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 µm) or *Hewlett-Packard* 6890 or 5890 series II, using a column of type HP 5 (*Hewlett-Packard*, 5% phenylmethylpolysiloxane; length: 15 m; diameter: 0.25 mm; film thickness: 0.25 µm).

High resolution mass spectra (HRMS) and low resolution mass spectra (MS) were recorded on *Finnigan* MAT 95Q or *Finnigan* MAT 90 instrument or JEOL JMS-700.

Infrared spectra were recorded on a *Perkin* 281 IR spectrometer and samples were measured neat (ATR, Smiths Detection DuraSample IR II Diamond ATR). The absorption bonds were reported in wave numbers (cm^{-1}) and abbreviations for intensity are as follows: vs (very strong; maximum intensity), s (strong; above 75% of max. intensity), m (medium; from 50% to 75% of max. intensity), w (weak; below 50% of max. intensity) as well as br (broad).

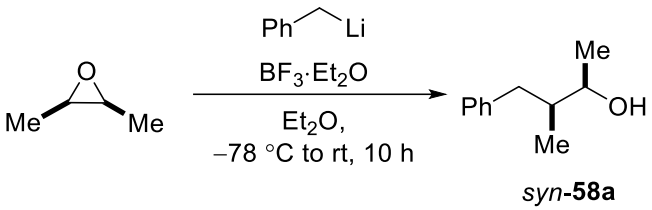
Stereoselective Synthesis and Retentive Trapping of α-Chiral Secondary Alkyllithiums Leading to Stereodefined α,β-Dimethyl Carboxylic Esters

Starting material synthesis



Benzyllithium

A dry and Ar flushed *Schlenk* flask was charged with TMEDA (5.0 mL, 33.4 mmol) in toluene (80 mL). ^{n}BuLi (14.0 mL, 2.4 M in hexane, 33.4 mmol) was added dropwise at room temperature and the resulting red solution was stirred for 2 h under reflux. The concentration was determined by titration with benzoic acid (0.41 M) and used for further experiments.



syn-**58a**

syn-**58a**

A dry and Ar flushed *Schlenk* flask was charged with *cis*-1,2-dimethyl ethylene oxide (1.0 mL, 11.1 mmol) in Et_2O (40 mL) and cooled to –60 °C. The solution of BnLi complexed with TMEDA (40 mL, 0.41 M in toluene, 16.7 mmol) was cannulated at –60 °C to the reaction mixture. After cooling down the reaction mixture to –78 °C, $BF_3{\cdot}Et_2O$ (2.1 mL, 16.7 mmol) was added and the resulting mixture was stirred at –78 °C for 20 min. After warming up to room temperature, it was stirred for additional 10 h. After quenching the reaction mixture with sat. aq. NH_4Cl solution, the reaction mixture was extracted with Et_2O (3×70 mL). The combined organic phase was dried over $MgSO_4$ and the solvents were evaporated. The crude

product was purified by column chromatography on silica gel with EtOAc/^{i}hexane = 1/4 to afford *syn*-**58a** (1.48 g, 81% yield, dr=1:99) as a colorless oil.

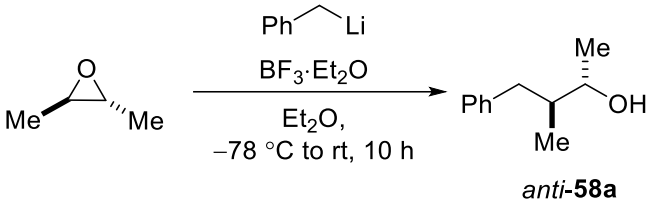
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32-7.23 (m, 2H), 7.23-7.14 (m, 3H), 3.70 (h, *J* = 6.2 Hz, 1H), 2.88 (dd, *J* = 13.4, 4.9 Hz, 1H), 2.35 (dd, *J* = 13.4, 9.3 Hz, 1H), 1.91-1.75 (m, 1H), 1.21 (d, *J* = 6.2 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ: 141.2, 129.3, 128.4, 125.9, 71.6, 42.4, 39.3, 19.9, 14.8.

MS (70 eV, EI) *m/z* (%): 164 (7) $[M]^{+\bullet}$, 146 (42), 131 (67), 91 (100), 77 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3356 (br, s), 2969 (w), 2928 (w), 2878 (w), 1495 (w), 1453 (w), 1378 (w), 1124 (w), 1085 (w), 1056 (w), 1030 (w), 1000 (w), 932 (w), 911 (w), 892 (w), 739 (m), 689 (vs).

HRMS (EI) *m/z*: calcd for **$C_{11}H_{16}O^{+\bullet}$** $[M]^{+\bullet}$: 164.1196, found 164.1194.



anti-**58a**

anti-**58a**

The *anti*-**58a** was synthesized according to the procedure for *syn*-**58a**, using *trans*-1,2-dimethyl ethylene oxide (1.0 mL, 11.1 mmol) as a starting material. The crude product was purified by column chromatography on silica gel with EtOAc/^{i}hexane = 1/4 to afford *anti*-**58a** (1.31 g, 72% yield, dr=99:1) as a colorless oil.

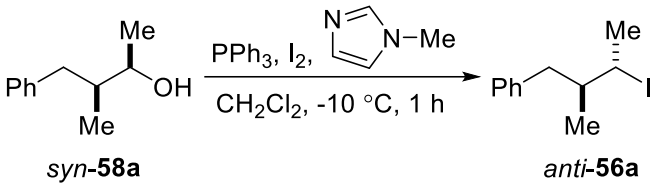
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32-7.24 (m, 2H), 7.23-7.15 (m, 3H), 3.77 (qd, *J* = 6.4, 3.8 Hz, 1H), 2.83 (dd, *J* = 13.3, 5.9 Hz, 1H), 2.40 (dd, *J* = 13.3, 9.0 Hz, 1H), 1.86-1.71 (m, 1H), 1.20 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ: 141.2, 129.3, 128.4, 125.9, 70.5, 41.9, 39.5, 20.7, 13.7.

MS (70 eV, EI) *m/z* (%): 164 (5) $[M]^{+\bullet}$, 146 (34), 114 (9), 91 (100), 77 (20).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3366 (br, s), 2969 (w), 2932 (w), 2878 (w), 1495 (w), 1453 (w), 1378 (w), 1144 (w), 1097 (w), 1078 (w), 1058 (w), 1030 (w), 993 (w), 928 (w), 913 (w), 893 (w), 736 (m), 698 (vs).

HRMS (EI) *m/z*: calcd for **$C_{11}H_{16}O^{+\bullet}$** $[M]^{+\bullet}$: 164.1196, found 164.1192.



syn-**58a** *anti*-**56a**

anti-**56a**

A dry and Ar-flushed *Schlenk*-flask was charged with a solution of I_2 (1.24 g, 4.9 mmol) in CH_2Cl_2 (25 mL) and cooled to −10 °C. PPh_3 (1.28 g, 4.9 mmol) was added at −10 °C and the resulting yellow suspension was stirred for 1 h at −10 °C. Then *N*-methylimidazole (0.39 mL, 4.9 mmol) was added. After 10 min of further stirring, *syn*-**58a** (0.50 g, 3.0 mmol, dr=1:99), dissolved in CH_2Cl_2 (5 mL), was added and the reaction mixture was stirred for 1 h at −10 °C. The reaction mixture was quenched with sat. aq. $NaHSO_3 \cdot Na_2S_2O_5$ solution[3] and it was extracted with CH_2Cl_2 (3×50 mL). The combined organic phase was dried over $MgSO_4$ and the solvents were evaporated at 30 °C.[4,5] The residue was triturated three times with a mixture of Et_2O/^{n}pentane = 1/4. The precipitate was filtered off and all organic phases were combined. The solvents were evaporated at 30 °C. The crude product was purified by chromatography on silica gel with ^{i}hexane to afford *anti*-**58a** (0.62 g, 74% yield, dr=99:1) as pale pink oil.

[3] Quenching with water or unsaturated ($NaHSO_4 \cdot Na_2S_2O_5$) aqueous solution sometimes cause epimerization of the product.

[4] Evaporation of higher temperature (>30 °C) sometimes cause epimerization of the product.

[5] Removal of triphenyl phosphine oxide before column chromatography is recommended to get higher yield of the product by washing and filtering the crude product with ether/pentane mixture.

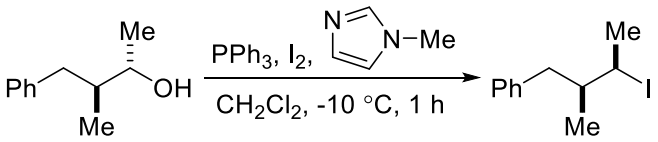
^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.32-7.24 (m, 2H), 7.23-7.15 (m, 3H), 3.77 (qd, *J* = 6.4, 3.8 Hz, 1H), 2.83 (dd, *J* = 13.3, 5.9 Hz, 1H), 2.40 (dd, *J* = 13.3, 9.0 Hz, 1H), 1.86-1.71 (m, 1H), 1.20 (d, *J* = 6.4 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 141.2, 129.3, 128.5, 126.3, 43.7, 43.2, 40.7, 26.9, 17.4.

MS (70 eV, EI) *m/z* (%): 274 (2) $[M]^{+\bullet}$, 147 (39), 115 (5), 91 (100), 65 (9).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3026 (w), 2965 (w), 2911 (w), 2853 (w), 1492 (w), 1452 (w), 1441 (w), 1378 (w), 1324 (w), 1265 (w), 1181 (w), 1103 (w), 1070 (w), 1030 (w), 1002 (w), 963 (w), 908 (w), 782 (w), 736 (s), 698 (vs).

HRMS (EI) *m/z*: calcd for **$C_{11}H_{15}I^{+\bullet}$** $[M]^{+\bullet}$: 274.0213, found 274.0207.



anti-**58a** *syn*-**56a**

syn-**56a**

The *syn*-**56a** was synthesized according to the procedure for *anti*-**58a**, using *anti*-**58a** (0.38 g, 2.3 mmol, dr=99:1) as a starting material. The crude product was purified by chromatography on silica gel with ^{i}hexane to afford *syn*-**56a** (0.30 g, 47% yield, dr=1:99) as pale pink oil.

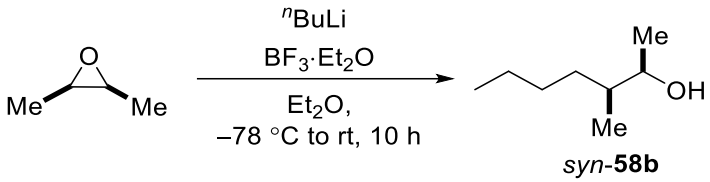
^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.33-7.25 (m, 2H), 7.23-7.13 (m, 3H), 7.34 (qd, *J* = 7.0, 3.9 Hz, 1H), 2.86 (dd, *J* = 13.5, 5.1 Hz, 1H), 2.39 (dd, *J* = 13.5, 9.0 Hz, 1H), 1.94 (d, *J* = 7.0 Hz, 3H), 1.80-1.67 (m, 1H), 0.96 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 140.3, 129.2, 128.5, 126.2, 44.1, 41.0, 38.3, 25.0, 18.2.

MS (70 eV, EI) *m/z* (%): 274 (2) $[M]^{+\bullet}$, 147 (40), 115 (5), 91 (100), 65 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3026 (w), 2964 (w), 2926 (w), 2857 (w), 1495 (w), 1453 (w), 1378 (w), 1270 (w), 1180 (w), 1166 (w), 1148 (w), 1097 (w), 1030 (w), 1006 (w), 961 (w), 908 (w), 801 (w), 783 (w), 737 (s), 698 (vs).

HRMS (EI) *m/z*: calcd for $\mathbf{C_{11}H_{15}I^{+\bullet}}$ $[M]^{+\bullet}$: 274.0213, found 274.0209.



syn-**58b**

syn-**58b**

According to the procedure for *syn*-**58a**, ^{n}BuLi solution (7.0 mL, 2.4 M in hexane, 16.7 mmol) and *cis*-1,2-dimethyl ethylene oxide (1.0 mL, 11.1 mmol) were used as substrates. The crude product was purified by column chromatography on silica gel with $Et_2O/^{n}$pentane = 1/3 to afford *syn*-**58b** (1.21 g, 84% yield, dr=1:99) as a colorless oil.

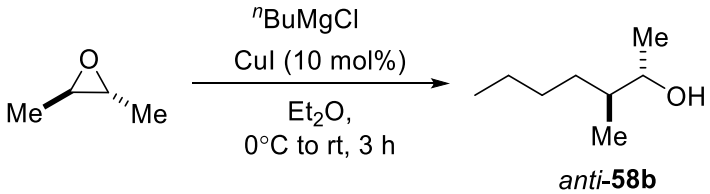
^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 3.66 (p, *J* = 6.2 Hz, 1H), 1.52 – 1.16 (m, 6H), 1.12 (d, *J* = 6.2 Hz, 3H), 1.10 – 1.02 (m, 1H), 0.93 – 0.81 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 71.9, 40.1, 32.4, 29.6, 23.2, 19.4, 14.6, 14.3.

MS (70 eV, EI) *m/z* (%): 129 (2) $[M-H]^{+\bullet}$, 115 (1), 113(3), 84 (7), 69 (10), 55 (26), 45 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3349 (br, m), 2958 (vs), 2926 (vs), 2874 (s), 2860 (s), 1458 (s), 1378 (s), 1329 (s), 1246 (m), 1212 (w), 1133 (m), 1104 (vs), 1074 (s), 1066 (s), 1052 (s), 995 (s), 964 (m), 922 (s), 895 (m), 882 (m), 814 (m), 778 (m), 728 (s), 664 (s).

HRMS (EI) *m/z*: calcd for $\mathbf{C_8H_{17}^{+\bullet}}$ $[M-OH]^{+\bullet}$: 113.1330, found 113.1311.



anti-**58b**

anti-**58b**

A dry and Ar flushed *Schlenk*-flask was charged with CuI (0.21 g, 1.1 mmol) in Et_2O (20 mL) and cooled down to 0 °C. ^{n}BuMgCl solution (10.1 mL, 1.2 M in THF, 12.2 mmol) was added dropwise at 0 °C. The reaction mixture turned black. Then c*is*-1,2-dimethyl ethylene oxide (1.0 mL, 11.1 mmol) was added dropwise at 0 °C. After warming up to room temperature, it was stirred for another 3 h. After quenching the reaction mixture with sat. aq. NH_4Cl solution, the reaction mixture was extracted with Et_2O (3×30 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by column chromatography on silica gel with Et_2O/^{n}pentane = 1/3 to afford *anti*-**58b** (1.25 g, 86% yield, dr=99:1) as a colorless oil.

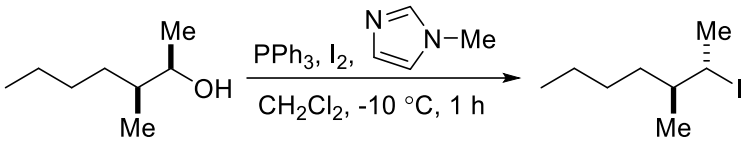
^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 3.69 (dd, *J* = 6.4, 4.3 Hz, 1H), 1.48 – 1.17 (m, 7H), 1.14 (d, *J* = 6.4 Hz, 3H), 1.12 – 1.05 (m, 1H), 0.93 – 0.82 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 71.5, 39.9, 32.5, 29.7, 23.1, 20.4, 14.3, 14.3.

MS (70 eV, EI) *m/z* (%): 115 (7) $[M\text{-}CH_3]^{+\bullet}$, 97 (13), 84 (58), 55 (30), 45 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3360 (br, m), 2959 (vs), 2927 (vs), 2874 (s), 2860 (s), 1460 (s), 1378 (s), 1346 (s), 1297 (m), 1245 (w), 1152 (m), 1102 (s), 1060 (s), 1040 (m), 1016 (m), 992 (s), 972 (m), 926 (s), 895 (m), 882 (m), 845 (w), 794 (w), 775 (m), 728 (s), 670 (m).

HRMS (EI) *m/z*: calcd for **$C_8H_{17}O^{+\bullet}$** $[M\text{-}H]^{+\bullet}$: 129.1274, found 129.1284.



syn-**58b** *anti*-**56b**

anti-**56b**

According to the procedure for *anti*-**56a**, *syn*-**58b** (0.60 g, 4.6 mmol, dr=1:99) was used as a starting material. The crude product was purified by chromatography on silica gel with *n*-pentane to afford *anti*-**56b** (0.45 g, 41% yield, dr=99:1) as colorless oil.

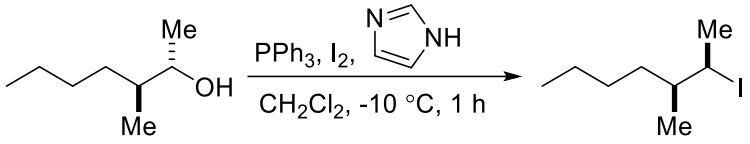
^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 4.37 (dd, *J* = 7.0, 2.9 Hz, 1H), 1.89 (d, *J* = 7.0 Hz, 3H), 1.39 – 1.12 (m, 6H), 0.89 (d, *J* = 6.6 Hz, 6H), 0.79 – 0.71 (m, 1H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ: 41.9, 41.0, 37.2, 29.3, 26.7, 22.9, 17.5, 14.3.

MS (70 eV, EI) *m/z* (%): 113 (100) $[M\text{-}I]^{+\bullet}$, 97 (21), 71 (88), 57 (95).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2959 (s), 2924 (s), 2872 (m), 2858 (m), 1456 (s), 1442 (s), 1378 (s), 1332 (w), 1324 (w), 1303 (w), 1293 (w), 1279 (w), 1245 (w), 1215 (w), 1204 (w), 1181 (vs), 1139 (s), 1114 (w), 1096 (w), 1048 (m), 1013 (w), 1004 (w), 990 (w), 961 (m), 910 (m), 895 (w), 859 (w), 806 (m), 781 (m), 763 (m), 728 (m), 700 (w), 665 (w), 658 (w).

HRMS (EI) *m/z*: calcd for **$C_4H_8I^{+\bullet}$** $[M\text{-}C_4H_9]^{+\bullet}$: 182.9665, found 182.9633.



anti-**58b** *syn*-**56b**

syn-**56b**

The compound *syn*-**56b** was prepared according to the described procedure[117] with some modifications. PPh_3 (0.91 g, 3.5 mmol) and imidazole (0.24 g, 3.5 mmol) were placed in a dry and Ar flushed *Schlenk* flask and were dissolved in CH_2Cl_2 (20 mL). The reaction mixture was cooled to 0 °C and I_2 (0.88 g, 3.5 mmol) was added portionwise. After stirring for 15 min at 0 °C *anti*-**s2** (0.30 g, 2.3 mmol, dr=99:1), dissolved in CH_2Cl_2 (3 mL), was added dropwise. The reaction mixture was stirred for 1 h at 0 °C and then was quenched with sat. aq. $NaHSO_3 \cdot Na_2S_2O_5$ solution[7] and it was extracted with CH_2Cl_2 (3×30 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated at 30 °C.[8] The crude product was purified by chromatography on silica gel with *n*-pentane to afford *syn*-**56b** (0.18 g, 33% yield, dr=1:99) as colorless oil.

[7] Quenching with water or unsaturated ($NaHSO_4$+$Na_2S_2O_5$) aqueous solution sometimes cause epimerization of the product.

[8] Evaporation of higher temperature (>30 °C) sometimes cause epimerization of the product.

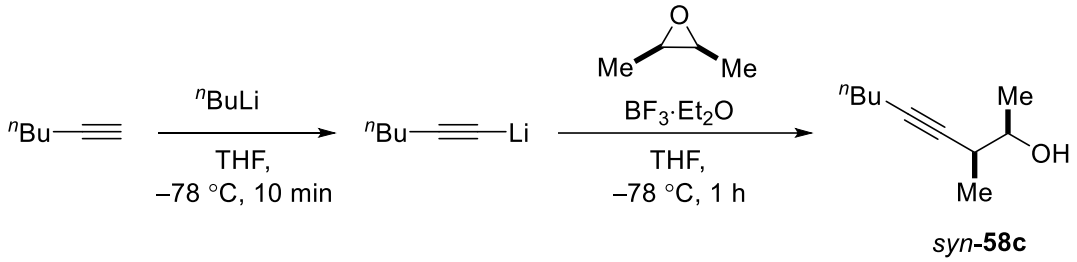
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.35 (qd, *J* = 7.0, 3.6 Hz, 1H), 1.84 (d, *J* = 7.0 Hz, 3H), 1.51 – 1.40 (m, 1H), 1.39 – 1.09 (m, 6H), 0.99 (d, *J* = 6.5 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 41.9, 40.2, 34.2, 29.6, 24.9, 23.0, 18.5, 14.2.

MS (70 eV, EI) *m/z* (%): 127 (7) $[I]^{+\bullet}$**,** 113 (100) $[M\text{-}I]^{+\bullet}$, 71 (71), 57 (45).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958 (vs), 2927 (vs), 2872 (m), 2858 (s), 1457 (s), 1378 (s), 1342 (w), 1324 (w), 1296 (w), 1246 (w), 1221 (w), 1174 (s), 1139 (s), 1117 (w), 1099 (s), 1064 (w), 1037 (w), 1017 (w), 1002 (w), 972 (w), 955 (w), 894 (w), 804 (w), 780 (w), 764 (w), 728 (w), 680 (vw), 661 (vw).

HRMS (EI) *m/z*: calcd for **$C_4H_8I^{+\bullet}$** $[M\text{-}C_4H_9]^{+\bullet}$: 182.9665, found 182.9676.



syn-**58c**

syn-**58c**

The compound *syn*-**58c** was prepared using the described procedure[93] with some modifications. A dry and Ar flushed *Schlenk* flask was charged with 1-hexyne (0.19 mL, 1.66 mmol) in THF (2 mL) and cooled to −78 °C. ^{n}BuLi solution (0.71 mL, 2.5 M in hexane, 1.77 mmol) was added dropwise at −78 °C. After stirring for 15 min at −78 °C, $BF_3{\cdot}OEt_2$ (0.22 mL, 1.77 mmol) was added dropwise at −78 °C and the reaction mixture was stirred for another 15 min at −78 °C. Then a solution of *cis*-1,2-dimethyl ethylene oxide (0.10 mL, 1.11 mmol) in THF (1 mL) was added dropwise and the reaction was stirred for 30 min at −78 °C and then quenched with sat. aq. NH_4Cl solution. The reaction mixture was extracted with Et_2O (3×5 mL), the combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by column chromatography on silica gel with EtOAc/^{i}hexane = 1/4 to afford *syn*-**58c** (154 mg, 90% yield, dr=1:99) as a colorless oil.

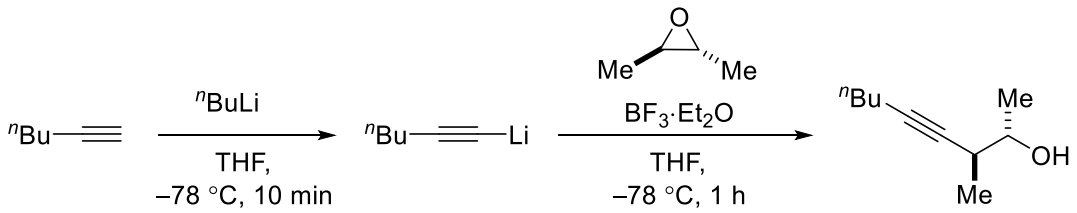
^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.56 (qd, *J* = 6.0, 5.7 Hz, 1H), 2.50 – 2.33 (m, 1H), 2.22 – 2.13 (m, 2H), 1.97 (d, *J* = 5.7 Hz, 1H), 1.52 – 1.34 (m, 4H), 1.21 (d, *J* = 6.0 Hz, 3H), 1.16 (d, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 83.7, 80.7, 71.1, 35.1, 31.3, 22.1, 20.9, 18.5, 17.9, 13.8.

MS (70 eV, EI) *m/z* (%): 139 (1) $[M\text{-}CH_3]^{+\bullet}$, 125 (2), 109 (1), 95 (27), 81 (15), 68 (100), 55 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3349 (w), 2960 (s), 2933 (s), 2874 (m), 2212 (vw), 1714 (w), 1677 (w), 1618 (w), 1454 (s), 1434 (m), 1397 (m), 1376 (s), 1344 (m), 1328 (m), 1299 (m), 1266 (m), 1252 (m), 1226 (m), 1174 (m), 1098 (vs), 1073 (s), 1012 (s), 998 (s), 964 (m), 955 (m), 913 (s), 876 (m), 854 (w), 745 (m), 728 (m), 710 (m), 680 (m).

HRMS (EI) *m/z*: calcd for $C_{10}H_{17}O^{+\bullet}$ $[M\text{-}H]^{+\bullet}$: 153.1279, found 153.1272.



anti-**58c**

anti-**58c**

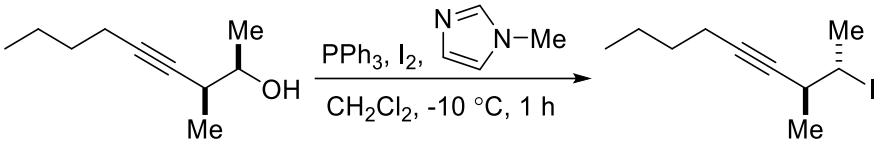
According to the procedure for *syn*-**58c**, *trans*-1,2-dimethyl ethylene oxide (0.1 mL, 1.11 mmol) was used as a staring material. The crude product was purified by chromatography on silica gel with EtOAc/^{i}hexane = 1/4 to afford *anti*-**58c** (145 mg, 85% yield, dr=99:1) as colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.69 (p, *J* = 6.1 Hz, 1H), 2.62 – 2.51 (m, 1H), 2.21 – 2.11 (m, 2H), 1.79 (s, 1H), 1.53 – 1.32 (m, 4H), 1.21 (d, *J* = 6.1 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ: 83.1, 81.1, 70.6, 34.3, 31.3, 22.1, 19.4, 18.5, 16.7, 13.8.

MS (70 eV, EI) *m/z* (%): 139 (1) $[M\text{-}CH_3]^{+\bullet}$, 125 (5), 97 (2), 95 (16), 81 (53), 68 (100), 55 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3357 (w), 2960 (s), 2931 (vs), 2874 (s), 1456 (s), 1435 (m), 1400 (m), 1376 (s), 1354 (m), 1328 (m), 1298 (m), 1250 (m), 1168 (w), 1127 (m), 1086 (s), 1008 (s), 972 (m), 962 (m), 910 (vs), 875 (w), 802 (w), 747 (w), 726 (m), 680 (m), 656 (m).

HRMS (EI) *m/z*: calcd for $C_{10}H_{18}O^{+\bullet}$ $[M\text{-}CH_3]^{+\bullet}$: 139.1123, found 139.1113.



syn-**58c** *anti*-**56c**

anti-**56c**

According to the procedure for *anti*-**56a**, *syn*-**56c** (0.60 g, 3.8 mmol, dr=1:99) was used as a starting material. The crude product was purified by chromatography on silica gel with *n*-pentane to afford *anti*-**56c** (0.17 g, 17% yield, dr=99:1) as pale pink oil.

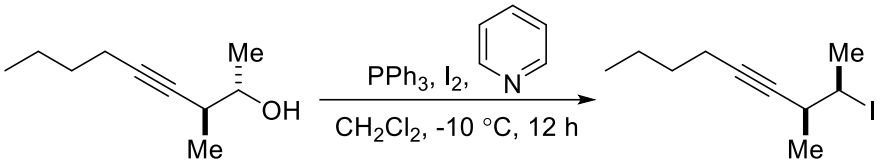
^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.14 (p, *J* = 6.8 Hz, 1H), 2.70 – 2.51 (m, 1H), 2.23 – 2.10 (m, 2H), 1.96 (d, *J* = 7.0 Hz, 3H), 1.53 – 1.36 (m, 4H), 1.24 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 83.3, 81.0, 77.2, 36.8, 34.2, 31.1, 26.0, 22.1, 21.3, 18.6, 13.8.

MS (70 eV, EI) *m/z* (%): 264 (2) $[M]^{+\bullet}$**,** 154 (3)**,** 137 (67), 95 (100), 81 (46), 67 (27), 55 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958 (s), 2931 (vs), 2872 (m), 2863 (m), 1448 (s), 1376 (s), 1354 (w), 1344 (m), 1330 (m), 1281 (m), 1261 (w), 1251 (w), 1183 (s), 1154 (s), 1134 (m), 1117 (m), 1095 (s), 1066 (m), 1044 (m), 998 (m), 970 (w), 960 (w), 951 (m), 930 (w), 898 (vw), 877 (w), 840 (w), 823 (w), 803 (w), 751 (w), 728 (w), 710 (w), 701 (w), 668 (vw), 660 (vw), 648 (vw), 640 (vw), 624 (w), 592 (vs), 567 (w), 558 (w).

HRMS (EI) *m/z*: calcd for **$C_{10}H_{17}I^{+\bullet}$** $[M]^{+\bullet}$: 264.0369, found 264.0344.



anti-**58c** *syn*-**56c**

syn-**56c**

The compound *syn*-**56c** was prepared using the described procedure for the synthesis of different iodides[118], method C, with some modifications. PPh_3 (0.96 g, 3.6 mmol) and pyridine (0.47 mL, 5.8 mmol) were placed in a dry and Ar flushed *Schlenk* flask and were dissolved in CH_2Cl_2 (25 mL). The reaction mixture was cooled to 0 °C and I_2 (0.93 g, 3.6 mmol) was added portion wise. After stirring for 15 min at 0 °C a solution of *anti*-**58c** (0.47 g, 3.0 mmol, dr=99:1) in CH_2Cl_2 (5 mL) at 0 °C dropwise and then the reaction mixture was stirred overnight at 0 °C. The reaction was quenched with sat. aq. $NaHSO_3 \cdot Na_2S_2O_5$ solution[10] and it was extracted with CH_2Cl_2 (3×30 mL). The organic phase was washed once with 1 M HCl solution and then with sat. aq. $NaHCO_3$ solution. The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated at 30 °C.[11] The crude product was purified by chromatography on silica gel with *n*-pentane to afford *syn*-**56c** (0.15 g, 19% yield, dr=1:99) as pale pink oil.

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.21 (qd, *J* = 6.8, 3.4 Hz, 1H), 2.37 – 2.26 (m, 1H), 2.20 – 2.13 (m, 2H), 1.95 (d, *J* = 6.9 Hz, 3H), 1.53 – 1.37 (m, 4H), 1.22 (d, *J* = 6.8 Hz, 3H), 0.91 (t, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 83.4, 81.0, 36.0, 35.9, 31.1, 26.4, 22.1, 21.5, 18.6, 13.8.

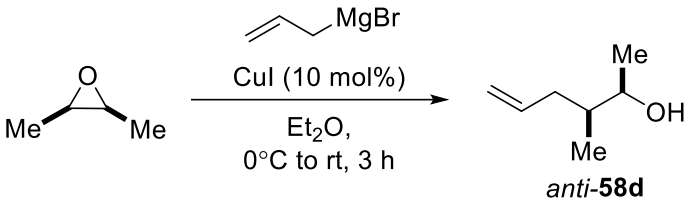
MS (70 eV, EI) *m/z* (%): 264 (3) $[M]^{+\bullet}$**,** 154 (4)**,** 137 (75), 95 (100), 81 (80), 67 (51), 55 (45).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958 (s), 2929 (vs), 2871 (m), 2860 (m), 1454 (s), 1376 (s), 1354 (w), 1333 (m), 1284 (s), 1250 (w), 1183 (m), 1170 (vs), 1147 (m), 1131 (w), 1107 (m), 1094 (s), 1056 (w), 1037 (w), 1010 (m), 991 (w), 972 (m), 940 (w), 931 (w), 898 (vw), 880 (vw), 846 (w), 828 (w), 803 (vw), 778 (vw), 749 (w), 727 (w), 706 (w), 658 (vw), 649 (vw), 642 (vw), 634 (vw), 603 (m), 596 (m), 568 (w), 553 (w).

HRMS (EI) *m/z*: calcd for $\mathbf{C_{10}H_{17}I^{+\bullet}}$ $[M]^{+\bullet}$: 264.0369, found 264.0347.

[10] Quenching with water or unsaturated ($NaHSO_4$+$Na_2S_2O_5$) aqueous solution sometimes cause epimerization of the product.

[11] Evaporation of higher temperature (>30 °C) sometimes cause epimerization of the product.



anti-**58d**

anti-**58d**

According to the procedure for *anti*-**58b**, *cis*-1,2-dimethyl ethylene oxide (1.0 mL, 11.1 mmol) was used as a starting material and allylmagnesium bromide was prepared according to the described procedure[119]. The crude product was purified by chromatography on silica gel with Et_2O/^{n}pentane = 1/4 to afford *anti*-**58d** (0.74 g, 58% yield, dr=1:99) as colorless oil with small impurities.

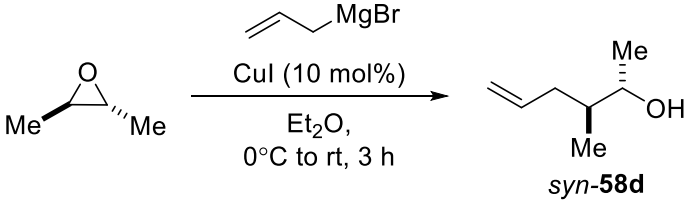
^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 5.93 – 5.69 (m, 1H), 5.09 – 4.96 (m, 2H), 3.71 – 3.60 (m, 1H), 2.30 – 2.19 (m, 1H), 1.98 – 1.87 (m, 1H), 1.64 – 1.54 (m, 1H), 1.41 (d, *J* = 3.8 Hz, 1H), 1.15 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 137.6, 116.1, 71.7, 40.1, 37.5, 20.0, 15.0.

MS (70 eV, EI) *m/z* (%): 99 (2) $[M\text{-}CH_3]^{+\bullet}$, 96 (24), 81 (63), 70 (39), 55 (77) 45 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3364 (m), 3077 (w), 2973 (m), 2929 (m), 2881 (m), 1700 (w), 1641 (m), 1570 (w), 1455 (m), 1412 (m), 1378 (m), 1298 (m), 1224 (w), 1153 (m), 1092 (m), 1056 (m), 994 (s), 968 (m), 946 (m), 909 (vs), 872 (m), 697 (m), 682 (m), 672 (m).

HRMS (EI) *m/z*: calcd for **$C_7H_{13}O^{+\bullet}$** $[M\text{-}H]^{+\bullet}$: 113.0961, found 113.1038.



syn-**58d**

syn-**58d**

According to the procedure for *anti*-**58b**, *trans*-1,2-dimethyl ethylene oxide (1.0 mL, 11.1 mmol) was used as a starting material. The crude product was purified by chromatography on

silica gel with Et_2O/^{n}pentane = 1/4 to afford *syn*-**s4** (0.54 g, 43% yield, dr=99:1) as colorless oil with small impurities.

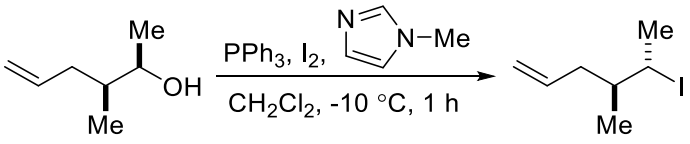
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.88 – 5.73 (m, 1H), 5.08 – 4.97 (m, 2H), 3.79 – 3.70 (m, 1H), 2.30 – 2.17 (m, 1H), 1.97 – 1.86 (m, 1H), 1.62 – 1.50 (m, 1H), 1.35 (s, 1H), 1.16 (d, *J* = 6.4 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 137.6, 116.1, 71.0, 39.7, 37.6, 20.4, 14.0.

MS (70 eV, EI) *m/z* (%): 99 (1) $[M\text{-}CH_3]^{+\bullet}$, 96 (13), 81 (30), 70 (32), 55 (67) 45 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3416 (m), 3077 (w), 2972 (s), 2882 (m), 1700 (s), 1641 (w), 1460 (m), 1410 (m), 1376 (s), 1146 (m), 1110 (m), 1082 (m), 1057 (m), 992 (s), 947 (m), 911 (vs), 888 (m), 870 (m), 838 (w), 789 (w), 761 (w), 672 (m).

HRMS (EI) *m/z*: calcd for **$C_7H_{12}^{+\bullet}$** $[M\text{-}H_2O]^{+\bullet}$: 96.0939, found 96.0963.



syn-**58d** *anti*-**56d**

anti-**56d**

According to the procedure for *anti*-**56a**, *syn*-**58d** (0.63 g, 5.5 mmol, dr=1:99) was used as a starting material. The crude product was purified by chromatography on silica gel with ^{n}pentane to afford *anti*-**58d** (0.51 g, 41% yield, dr=97:3) as pale pink oil.

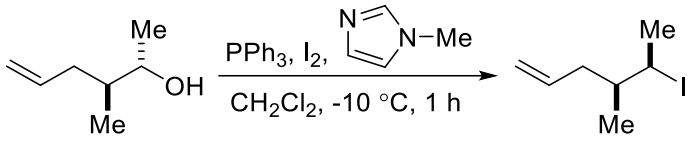
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.87 – 5.56 (m, 1H), 5.17 – 5.00 (m, 2H), 4.35 (qd, *J* = 7.1, 2.8 Hz, 1H), 2.15 – 1.94 (m, 2H), 1.91 (d, *J* = 7.1 Hz, 3H), 0.92 (d, *J* = 6.3 Hz, 3H), 0.90 – 0.80 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 136.3, 117.0, 41.9, 40.8, 40.7, 26.8, 17.3.

MS (70 eV, EI) *m/z* (%): 127 (2) $[I]^{+\bullet}$**,** 97 (25)**,** 81 (10), 67 (3), 55 (44), 45 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3077 (w), 2966 (m), 2912 (w), 2860 (w), 2840 (w), 1834 (vw), 1641 (w), 1439 (m), 1415 (w), 1378 (m), 1324 (w), 1304 (w), 1298 (w), 1261 (w), 1221 (w), 1182 (s), 1159 (w), 1131 (m), 1074 (w), 1064 (w), 1047 (w), 1008 (w), 992 (m), 967 (w), 949 (w), 913 (vs), 878 (w), 811 (w), 782 (w), 632 (m), 605 (w), 578 (s), 552 (w).

HRMS (EI) *m/z*: calcd for **$C_7H_{13}I^{+\bullet}$** $[M]^{+\bullet}$: 224.0056, found 223.9996.



anti-**58d** *syn*-**56d**

syn-**56d**

According to the procedure for *anti*-**56a**, *anti*-**58d** (0.38 g, 3.3 mmol, dr=99:1) was used as a starting material. The crude product was purified by chromatography on silica gel with ^{n}pentane to afford *syn*-**3d** (0.23 g, 31% yield, dr=5:95) as pale pink oil.

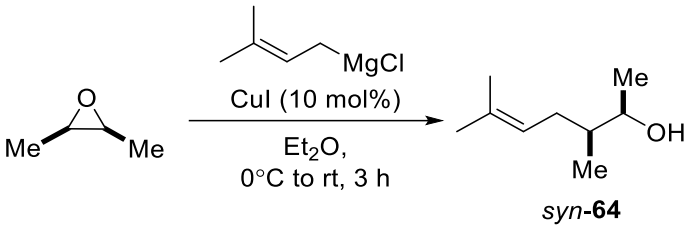
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.85 – 5.67 (m, 1H), 5.12 – 4.98 (m, 2H), 4.41 – 4.26 (m, 1H), 2.31 – 2.20 (m, 1H), 1.99 – 1.89 (m, 1H), 1.87 (d, *J* = 7.1 Hz, 3H), 1.56 – 1.46 (m, 1H), 1.00 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 136.4, 116.8, 41.8, 39.3, 38.4, 24.9, 18.1.

MS (70 eV, EI) *m/z* (%): 127 (2) $[I]^{+\bullet}$**,** 97 (67)**,** 81 (6), 67 (4), 55 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3077 (w), 2965 (m), 2922 (w), 2874 (w), 2842 (w), 1834 (vw), 1641 (m), 1451 (m), 1442 (m), 1415 (w), 1379 (m), 1330 (w), 1264 (w), 1235 (w), 1222 (vw), 1180 (m), 1161 (m), 1134 (m), 1095 (m), 1031 (w), 993 (s), 972 (w), 913 (vs), 888 (w), 877 (w), 810 (w), 782 (w), 681 (vw), 628 (w), 580 (s).

HRMS (EI) *m/z*: calcd for **$C_7H_{13}I^{+\bullet}$** $[M]^{+\bullet}$: 224.0056, found 224.0028.



syn-**64**

syn-**64**

According to the procedure for *anti*-**58b**, *cis*-1,2-dimethyl ethylene oxide (1.0 mL, 11.1 mmol) was used as a starting material and prenylmagnesium chloride was prepared according to the described procedure[102]. The crude product was purified by chromatography on silica gel with Et_2O/^{n}pentane = 1/4 to afford *syn*-**64** (0.74 g, 98% yield, dr=1:99) as colorless oil.

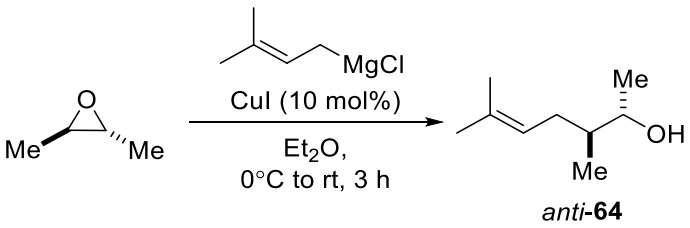
^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 5.10 – 5.24 (m, 1H), 3.73 – 3.57 (m, 1H), 2.17 – 2.06 (m, 1H), 1.93 – 1.82 (m, 1H), 1.72 – 1.68 (m, 3H), 1.62 (s, 3H), 1.58 – 1.49 (m, 1H), 1.48 (d, *J* = 4.3 Hz, 1H), 1.14 (d, *J* = 6.3 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 132.7, 123.1, 72.0, 41.1, 31.6, 26.0, 19.9, 18.0, 15.2.

MS (70 eV, EI) *m/z* (%): 142 (28) $[M]^{+\bullet}$, 124 (26), 109 (100), 95 (37), 85 (39), 69 (45), 55 (43).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3354 (m), 2969 (s), 2927 (s), 2878 (s), 1453 (s), 1377 (vs), 1330 (m), 1262 (m), 1156 (m), 1112 (s), 1083 (vs), 1050 (s), 1002 (s), 985 (s), 967 (m), 927 (s), 898 (s), 880 (s), 841 (m), 802 (m), 792 (m), 773 (m), 752 (m), 666 (s), 657 (s).

HRMS (EI) *m/z*: calcd for **$C_9H_{18}O^{+\bullet}$** $[M]^{+\bullet}$: 142.1352, found 142.1359.



anti-**64**

anti-**64**

According to the procedure for *anti*-**58b**, *trans*-1,2-dimethyl ethylene oxide (1.0 mL, 11.1 mmol) was used as a starting material. The crude product was purified by chromatography on

silica gel with Et_2O/^{n}pentane = 1/4 to afford *anti*-**64** (0.70 g, 74% yield, dr=99:1) as colorless oil.

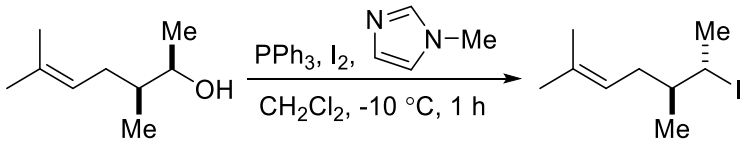
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.20 – 5.09 (m, 1H), 3.80 – 3.67 (m, 1H), 2.16 – 2.04 (m, 1H), 1.93 – 1.81 (m, 1H), 1.73 – 1.67 (m, 3H), 1.62 (s, 3H), 1.56 – 1.44 (m, 1H), 1.33 (s, 1H), 1.16 (d, *J* = 6.4 Hz, 3H), 0.88 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 132.7, 123.1, 71.2, 40.5, 31.6, 26.0, 20.6, 18.0, 14.1.

MS (70 eV, EI) *m/z* (%):142 (24) $[M]^{+\bullet}$, 124 (21), 109 (100), 95 (17), 85 (33), 69 (75), 55 (74).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3366 (m), 2967 (vs), 2925 (s), 2878 (s), 2858 (m), 1452 (s), 1376 (vs), 1260 (m), 1144 (m), 1115 (s), 1084 (s), 1072 (vs), 1048 (s), 1008 (s), 993 (s), 927 (s), 901 (m), 890 (m), 878 (m), 842 (m), 803 (m), 775 (m), 680 (m), 672 (m), 664 (m), 659 (m).

HRMS (EI) *m/z*: calcd for **$C_9H_{18}O^{+\bullet}$** $[M]^{+\bullet}$: 142.1352, found 142.1361.



syn-**64** *anti*-**65**

anti-**65**

According to the procedure for *anti*-**56a**, *syn*-**64** (0.36 g, 2.5 mmol, dr=1:99) was used as a starting material. The crude product was purified by chromatography on silica gel with ^{n}pentane to afford *anti*-**65** (0.32 g, 50% yield, dr=97:3) as pale pink oil with traces of elimination product.

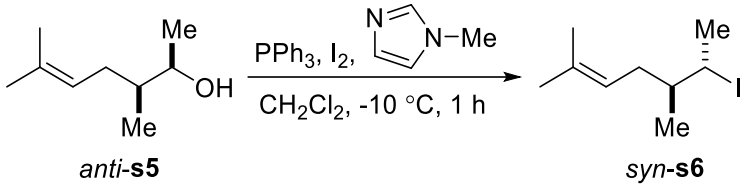
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5.10 – 5.01 (m, 1H), 4.39 (qd, *J* = 7.0, 2.9 Hz, 1H), 2.10 – 1.83 (m, 5H), 1.72 – 1.69 (m, 3H), 1.67 – 1.65 (m, 3H), 0.90 (d, *J* = 6.4 Hz, 3H), 0.82 – 0.71 (m, 1H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 133.7, 122.1, 42.0, 41.4, 36.1, 27.0, 26.0, 18.4, 17.6.

MS (70 eV, EI) *m/z* (%): 252 (7) $[M]^{+\bullet}$, 125 (27), 95 (7), 83 (16), 69 (100), 55 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2964 (s), 2925 (m), 2911 (m), 2858 (m), 1441 (s), 1376 (s), 1321 (m), 1261 (w), 1182 (vs), 1139 (m), 1131 (m), 1116 (m), 1094 (m), 1004 (w), 984 (w), 962 (m), 890 (w), 843 (m), 791 (w), 773 (w), 757 (m).

HRMS (EI) *m/z*: calcd for **$C_9H_{17}I^{+\bullet}$** $[M]^{+\bullet}$: 252.0369, found 252.0357.



anti-**s5** *syn*-**s6**

syn-**65**

According to the procedure for *anti*-**56a**, *anti*-**65** (0.23 g, 1.62 mmol, dr=99:1) was used as a starting material. The crude product was purified by chromatography on silica gel with ^{n}pentane to afford *syn*-**s6** (100 mg, 25% yield, dr=1:99) as pale pink oil.

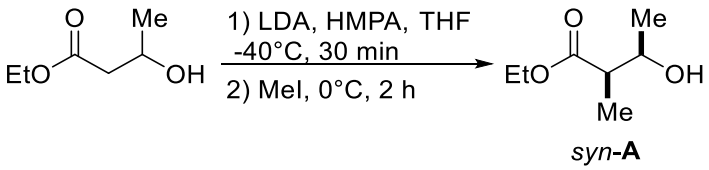
^{1}H NMR (400 MHz, $CDCl_3$) δ: 5 5.17 – 5.04 (m, 1H), 4.35 (qd, *J* = 7.0, 4.0 Hz, 1H), 2.20 – 2.10 (m, 1H), 1.92 – 1.82 (m, 4H), 1.73 – 1.68 (m, 3H), 1.63 – 1.60 (m, 3H), 1.51 – 1.41 (m, 1H), 0.98 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 133.3, 122.2, 42.9, 39.1, 33.4, 26.0, 24.9, 18.2, 18.1.

MS (70 eV, EI) *m/z* (%): 252 (33) $[M]^{+\bullet}$, 183 (8), 125 (38), 95 (4), 83 (16), 69 (100), 55 (18).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2965 (s), 2925 (s), 2915 (s), 2874 (m), 1451 (s), 1376 (vs), 1361 (m), 1179 (m), 1165 (m), 1145 (s), 1134 (s), 1117 (s), 1094 (s), 1076 (m), 1024 (s), 981 (s), 973 (s), 911 (m), 904 (m), 888 (m), 875 (m), 842 (m), 773 (m).

HRMS (EI) *m/z*: calcd for **$C_9H_{17}I^{+\bullet}$** $[M]^{+\bullet}$: 252.0369, found 252.0377.

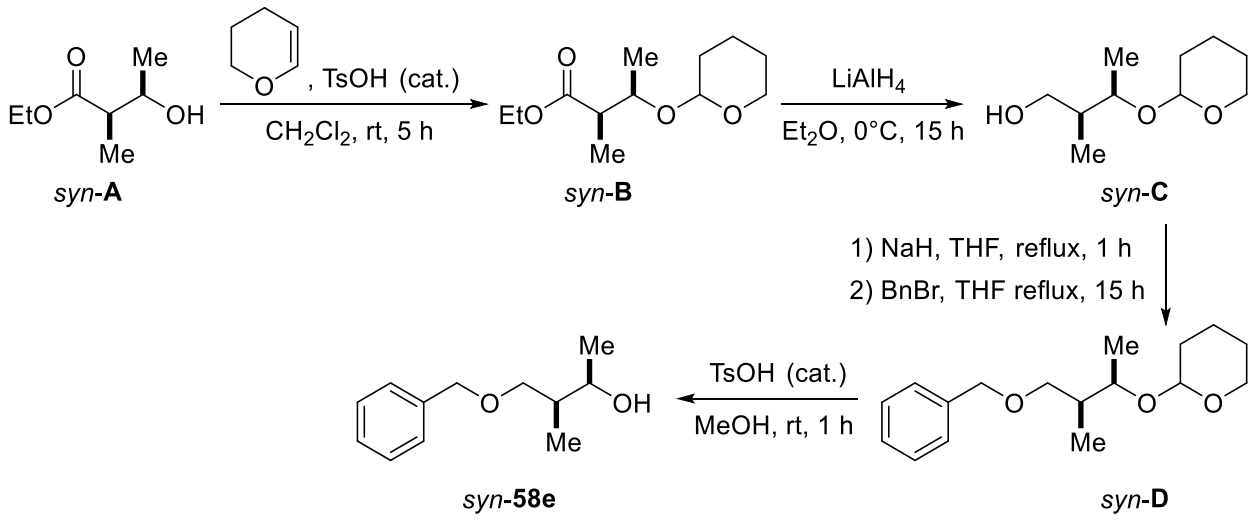


syn-**A**

syn-**A**

The alcohol *syn*-**A** was prepared according to the literature[120] with some modifications. ^{n}BuLi (20 mL, 2.5 M, 50 mmol) was added dropwise to a solution of diisopropylamine (6.7 mL, 47.7 mmol) in THF (50 mL) at −78 °C. The resulted solution was warmed up to −15 °C and it was stirred for 1 h at this temperature. To the cooled to −78 °C solution, a solution of ethyl 3-hydroxybutyrate (3.0 g, 22.7 mmol) in THF (15 mL) and HMPA (6.8 mL) was slowly added via cannula. The mixture was warmed up to −40 °C and stirred for 30 min before it was cooled back to −78 °C and iodomethane (1.77 mL, 28.4 mmol) was added. The reaction mixture was stirred for 2.5 h at 0 °C and then it was quenched with sat. aq. NH_4Cl solution. 1 M HCl solution was then added until pH = 7 was reached and the product was extracted with Et_2O (3×50 mL). The organic phases were dried over $MgSO_4$ and evaporated. The yellowish oil, obtained after the work-up, was filtered through a pad of silica gel and washed few times with Et_2O. The solution was concentrated *in vacuo* and the residue was distilled (147-148 °C/77 mbar) to give *syn*-**A** as a colorless oil (2.41 g, 73% yield, d.r. = 1:99). The obtained analytical data is consistent with the reported one[120].

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.17 (q, *J* = 7.2 Hz, 2H), 3.88 (p, *J* = 6.5 Hz, 1H), 2.52 – 2.37 (m, 1H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.22 (d, *J* = 6.5 Hz, 3H), 1.19 (d, *J* = 7.2 Hz, 3H).



syn-**58e**

The alcohol *syn*-**58e** was prepared according to the literature[121] starting from *syn*-**A**. To a solution of *syn*-**A** (1.56 g, 10.7 mmol) and dihydropyran (1.8 mL, 19.2 mmol) in CH_2Cl_2 (15

mL) was added TsOH (30 mg). The reaction mixture was stirred for 5 h at room temperature. The mixture was diluted with Et_2O (20 mL), washed with sat. aq. $NaHCO_3$ solution and water. The organic phases were separated, dried over $MgSO_4$ and evaporated. The resulted brownish oil was filtered through a pad of silica gel and washed few times with Et_2O. The solution was concentrated *in vacuo*. The crude product *syn*-**B** was obtained as yellowish oil (1.7 g, 70% yield) and it was used for the next step without any additional purification.

A solution of *syn*-**B** (1.7 g, 7.4 mmol) in Et_2O (15 mL) was dropwise added to a suspension of $LiAlH_4$ (400 mg, 10.5 mmol) in Et_2O (30 mL) at 0 °C. The reaction mixture was warmed up to room temperature and stirred overnight. Then the reaction mixture was cooled back to 0 °C and $Na_2SO_4 \cdot 10H_2O$ was added until the suspension became white and no bubbling was observed. The residue was filtered off and washed with Et_2O. The resulted solution was evaporated and concentrated *in vacuo*. The crude product *syn*-**C** was obtained as an oil (1.4 g, 99% yield) and was used later without any additional purification.

To a stirred suspension of NaH (480 mg, 60% suspension in mineral oil, 11.8 mmol) in THF (16 mL) was added a solution of *syn*-**C** (1.4 g, 7.4 mmol) in THF (20 mL) at room temperature. The reaction mixture was refluxed for 1 h, then cooled to room temperature and a solution of BnBr (1.77 g, 10.4 mmol) in THF (6 mL) was added. The resulting reaction mixture was refluxed overnight. After cooling to room temperature, the reaction mixture was poured into ice-water. The water phase was extracted with Et_2O (3×50 mL), the organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. The resulted yellowish oil (*syn*-**D**) was used in the next step without any purification.

To a mixture of crude *syn*-**D** and MeOH (15 mL) was added TsOH (30 mg) at room temperature. The reaction mixture became homogeneous in 1 h. After that, $NaHCO_3$ (50 mg) was added and the reaction mixture was concentrated in vacuo to remove MeOH. The formed residue was diluted with water (10 mL) and the aqueous phase was extracted with Et_2O (3×15 mL). The solvents were evaporated and the crude product was purified by flash column chromatography on silica gel with Et_2O/^{i}hexane = 1/3→1/2. The alcohol *syn*-**58e** was obtained as a colorless oil (0.95 g, 45% yield over 4 steps, dr=5:95).

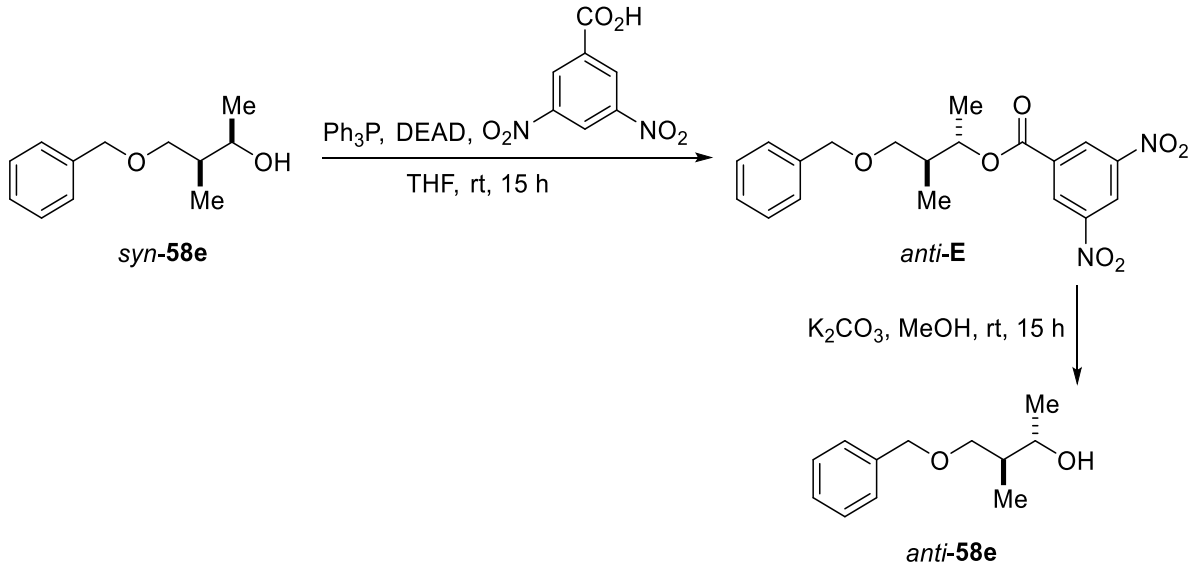
^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.40 – 7.27 (m, 5H), 4.53 (s, 2H), 3.70 (dq, *J* = 7.5, 6.2 Hz, 1H), 3.60 (dd, *J* = 9.2, 4.2 Hz, 1H), 3.45 (dd, *J* = 9.2, 8.2 Hz, 1H), 2.75 (s, 2H), 1.87 – 1.74 (m, 1H), 1.17 (d, *J* = 6.2 Hz, 3H), 0.86 (d, *J* = 7.0 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 137.9, 128.6, 127.9, 127.8, 75.8, 73.6, 72.8, 40.2, 21.3, 13.8.

MS (70 eV, EI) *m/z* (%): 194 (1) $[M]^{+\bullet}$**,** 176 (14)**,** 161 (2), 147 (3), 132 (4), 120 (12), 107 (38), 91 (100), 70 (23), 55 (9).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 3421 (w), 2968 (w), 2858 (w), 1496 (w), 1453 (m), 1376 (m), 1364 (m), 1309 (w), 1275 (w), 1206 (w), 1087 (s), 1073 (s), 1028 (m), 1002 (m), 971 (m), 956 (m), 925 (m), 905 (m), 890 (m), 818 (w), 735 (s), 714 (m), 697 (vs).

HRMS (EI) ***m/z*:** calcd for **$C_{12}H_{18}O_2^{+\bullet}$** $[M]^{+\bullet}$: 194.1301, found 194.1303.



syn-**58e** *anti*-**E** *anti*-**58e**

anti-**58e**

The alcohol *anti*-**58e** was prepared according to the literature[121] starting from *syn*-**58e** in 2 steps. To a solution of *syn*-**58e** (0.42 g, 2.2 mmol), Ph_3P (1.13 g, 4.3 mmol) and 3,5-dinintrobenzoic acid (0.92 g, 4.3 mmol) in THF (10 mL) was added dropwise a solution of diethyl azodicarboxylate (DEAD, 1.3 mL, 40% in toluene, 4.3 mmol) at 0 °C. Then the reaction mixture was warmed up to room temperature and stirred overnight. Then it was concentrated in vacuo and the residue was filtered through a pad of silica gel using CH_2Cl_2 as a solvent. The solvent was evaporated and the residue was chromatographed over silica gel with EtOAc/*i*-hexane = 1/6. The product *anti*-**E** was obtained with small impurities (0.68 g, 82% yield).

To the solution of compound *anti*-**E** (0.58 g, 1.5 mmol) in MeOH (10 mL) was added K_2CO_3 (0.79 g, 5.7 mmol) at room temperature. The reaction mixture was stirred overnight. Then it was treated with cold sat. aq. NH_4Cl solution and the water phase was extracted with Et_2O (3×20 mL). The organic phases were dried over $MgSO_4$ and the solvent was evaporated. The residue was purified by flash column chromatography with Et_2O/^{i}hexane = 1/2 to give the product (0.25 g, 86% yield, dr=96:4).

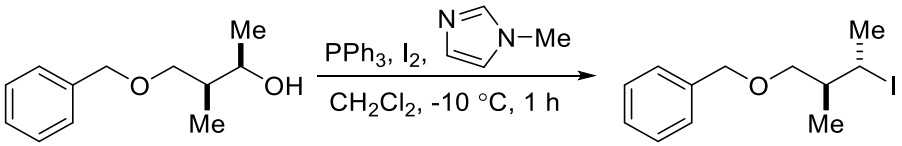
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.39 – 7.26 (m, 5H), 4.51 (s, 2H), 3.96 (qd, *J* = 6.5, 2.8 Hz, 1H), 3.52 (d, *J* = 5.7 Hz, 2H), 1.91 (qtd, *J* = 7.1, 5.7, 2.8 Hz, 1H), 1.15 (d, *J* = 6.5 Hz, 3H), 0.92 (d, *J* = 7.1 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 138.1, 128.6, 127.9, 127.8, 74.4, 73.6, 70.5, 39.1, 19.7, 11.4.

MS (70 eV, EI) *m/z* (%): 194 (1) $[M]^{+\bullet}$**,** 176 (7)**,** 132 (2), 108 (38), 91 (100), 70 (39), 55 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3428 (w), 3399 (w), 3344 (w), 3300 (vw), 2968 (w), 2877 (w), 1496 (w), 1453 (m), 1409 (w), 1364 (m), 1313 (w), 1274 (m), 1205 (w), 1174 (w), 1148 (m), 1091 (s), 1069 (s), 1027 (m), 1018 (m), 1001 (m), 958 (w), 934 (w), 920 (m), 905 (m), 892 (m), 817 (w), 805 (w), 797 (w), 734 (s), 713 (m), 696 (vs), 676 (m), 668 (m).

HRMS (EI) *m/z*: calcd for **$C_{12}H_{18}O_2^{+\bullet}$** $[M]^{+\bullet}$: 194.1301, found 194.1305.



syn-**58e** *anti*-**56e**

anti-**56e**

According to the procedure for *anti*-**56a**, *syn*-**58e** (0.50 g, 2.6 mmol, dr=5:95) was used as a starting material. The crude product was purified by chromatography on silica gel with Et_2O/^{n}pentane = 1/50 to afford *anti*-**3e** (0.68 g, 87% yield, dr=96:4) as pale pink oil with traces of elimination product.

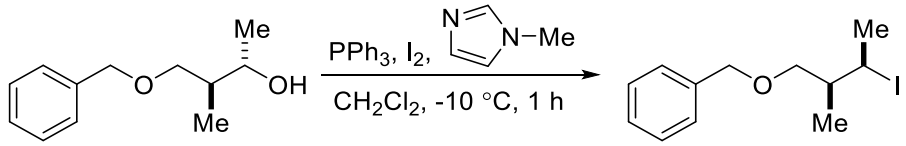
^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 – 7.27 (m, 5H), 4.69 (qd, *J* = 7.1, 2.8 Hz, 1H), 4.52 (d, *J* = 5.3 Hz, 2H), 3.37 (dd, *J* = 9.3, 5.3 Hz, 1H), 3.24 (dd, *J* = 9.3, 8.3 Hz, 1H), 1.92 (d, *J* = 7.1 Hz, 3H), 1.10 – 0.98 (m, 1H), 0.88 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 138.4, 128.5, 127.9, 127.8, 75.8, 73.5, 41.1, 37.6, 26.7, 14.3.

MS (70 eV, EI) *m/z* (%): 177 (1) $[M\text{-}I]^{+\bullet}$**,** 159 (4)**,** 145 (3), 121 (6), 105 (5), 91 (100), 65(4).

IR (ATR) $\tilde{\nu}$ **(cm^{-1}):** 2962 (w), 2856 (w), 1495 (w), 1452 (m), 1379 (m), 1362 (m), 1331 (w), 1316 (w), 1274 (w), 1188 (m), 1170 (w), 1135 (m), 1096 (s), 1048 (w), 1028 (m), 996 (w), 959 (w), 954 (w), 905 (w), 817 (w), 778 (w), 733 (s), 695 (vs), 668 (w).

HRMS (EI) *m/z*: calcd for **$C_{12}H_{17}IO^{+\bullet}$** $[M]^{+\bullet}$: 304.0319, found 304.0330.



anti-**58e** *syn*-**56e**

syn-**56e**

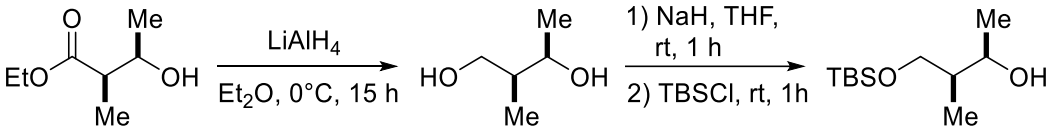
According to the procedure for *anti*-**56a**, *anti*-**58e** (0.20 g, 1.0 mmol, dr=96:4) was used as a starting material. The crude product was purified by chromatography on silica gel with Et_2O/^{n}pentane = 1/50 to afford *syn*-**3e** (0.15 g of mixture, 32% calculated yield, 70 wt% dr=5:95) as pale pink oil with elimination product. It was used without any additional purification for the next reactions.

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 7.37 – 7.28 (m, 5H), 4.54 – 4.46 (m, 3H), 3.49 (dd, *J* = 9.4, 6.5 Hz, 1H), 3.34 (dd, *J* = 9.4, 5.9 Hz, 1H), 1.98 – 1.90 (m, 1H), 1.87 (d, *J* = 7.1 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 138.4, 128.5, 127.9, 127.8, 76.5, 73.3, 42.4, 34.4, 24.9, 15.8.

MS (70 eV, EI) *m/z* (%): 177 (1) $[M\text{-}I]^{+\bullet}$**,** 159 (7)**,** 145 (3), 121 (5), 105 (5), 91 (100), 65(4).

HRMS (EI) *m/z*: calcd for **$C_{12}H_{17}IO^{+\bullet}$** $[M]^{+\bullet}$: 304.0319, found 304.0308.



syn-**A** *syn*-**F** *syn*-**58f**

syn-**58f**

The alcohol *syn*-**58f** was prepared starting from *syn*-**A**. A solution of *syn*-**A** (1.0 g, 6.8 mmol) in Et_2O (5 mL) was added dropwise to a suspension of $LiAlH_4$ (521 mg, 13.7 mmol) in Et_2O (25 mL) at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 5 h. The reaction mixture was cooled back to 0 °C and $Na_2SO_4 \cdot 10H_2O$ was added until the suspension became white and no bubbling was observed. The residue was filtered off and washed with Et_2O. The resulted solution was evaporated and concentrated *in vacuo*. The crude product *syn*-**F** was obtained as an oil (0.71 g, 99% yield) and was used later without any additional purification.

To a suspension of NaH (300 mg, 60% suspension in mineral oil, 7.5 mmol) in THF (20 mL) was added a solution of diol *syn*-**F** (0.71 g, 6.8 mmol) in THF (5 mL) at room temperature. The reaction mixture was stirred for 1 h and then TBSCl (1.03 g, 6.8 mmol) was added. The reaction mixture was stirred at room temperature for 2 h before it was cooled to 0 °C and diluted with Et_2O (50 mL) and quenched with water. The phases were separated and the water phase was extracted with Et_2O (2×50 mL). The organic phase was dried over $MgSO_4$ and evaporated. The residue was purified with column chromatography with Et_2O/^{i}hexane = 1/4 to give the product *syn*-**58f** as a colorless oil (1.20 g, 81% yield, dr=5:95).

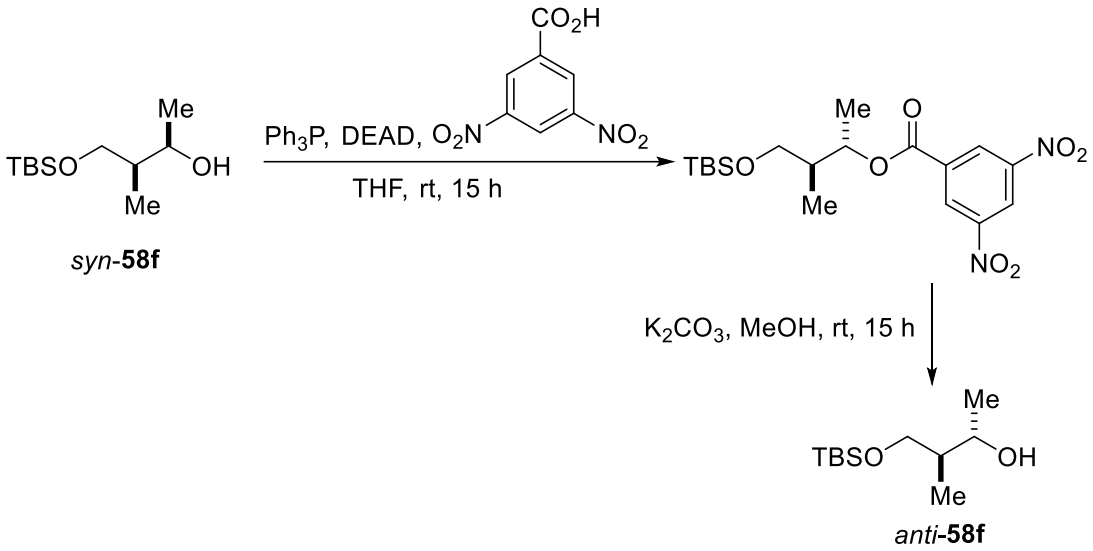
^{1}H NMR (400 MHz, $CDCl_3$) δ: 3.77 (dd, *J* = 10.0, 4.1 Hz, 1H), 3.69 (dq, *J* = 7.8, 6.3 Hz, 1H), 3.55 (dd, *J* = 10.0, 8.5 Hz, 1H), 1.71 – 1.58 (m, 1H), 1.17 (d, *J* = 6.3 Hz, 3H), 0.90 (s, 9H), 0.80 (d, *J* = 6.9 Hz, 3H), 0.08 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 73.4, 69.2, 41.5, 26.0, 25.8, 21.5, 18.2, 13.5, -5.4, -5.5.

MS (70 eV, EI) *m/z* (%): 203 (4) $[M\text{-}CH_3]^{+\bullet}$**,** 161 (22)**,** 143 (5), 119 (11), 105 (90), 75 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3335 (w), 2957 (m), 2930 (m), 2885 (w), 2858 (w), 1472 (w), 1463 (w), 1378 (w), 1362 (w), 1325 (w), 1254 (m), 1076 (m), 1031 (m), 1006 (m), 956 (w), 938 (w), 921 (w), 873 (m), 834 (vs), 815 (m), 774 (s), 667 (m).

HRMS (EI) *m/z*: calcd for $\mathbf{C_{10}H_{23}O_2Si^{+\bullet}}$ $[M\text{-}CH_3]^{+\bullet}$: 203.1462, found 203.1462.



anti-**58f**

According to the procedure for *anti*-**58e**, *syn*-**58f** (0.43 g, 2.0 mmol, dr=4:96) was used as a starting material. The crude product after 2 steps was purified by chromatography on silica gel with Et_2O/^{i}hexane = 1/4 to afford *anti*-**58f** (0.23 g of mixture, 58%, dr=99:1) as colorless oil.

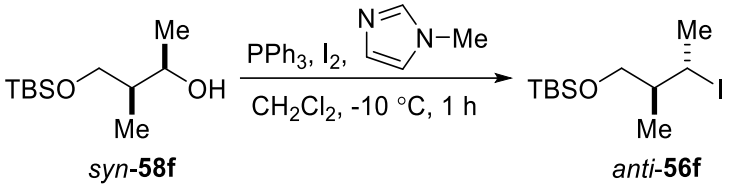
^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 3.98 (qd, *J* = 6.5, 2.6 Hz, 1H), 3.74 (dd, *J* = 9.9, 4.1 Hz, 1H), 3.67 (dd, *J* = 9.9, 6.1 Hz, 1H), 1.81 – 1.70 (m, 1H), 1.16 (d, *J* = 6.5 Hz, 3H), 0.92 – 0.85 (m, 12H), 0.07 (s, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 71.1, 68.0, 40.0, 26.0, 19.7, 18.3, 10.8, -5.5, -5.5.

MS (70 eV, EI) *m/z* (%): 203 (2) $[M\text{-}CH_3]^{+\bullet}$**,** 161 (17)**,** 143 (3), 119 (9), 105 (52), 89 (5), 75 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3444 (vw), 2957 (w), 2929 (m), 2858 (w), 1472 (w), 1463 (w), 1390 (w), 1362 (w), 1253 (m), 1084 (m), 1016 (m), 1005 (m), 938 (w), 884 (w), 833 (vs), 814 (m), 774 (s), 730 (w), 722 (w), 678 (w), 666 (m).

HRMS (EI) *m/z*: calcd for $\mathbf{C_{11}H_{25}O_2Si^{+\bullet}}$ $[M\text{-}H]^{+\bullet}$: 217.1618, found 217.1611.



syn-**58f** *anti*-**56f**

anti-**56f**

According to the procedure for *anti*-**56a**, *syn*-**58f** (0.50 g, 2.3 mmol, dr=5:95) was used as a starting material. The crude product was purified by chromatography on silica gel with ^{i}hexane to afford *anti*-**56f** (0.38 g, 51% yield, dr=97:3) as colorless oil.

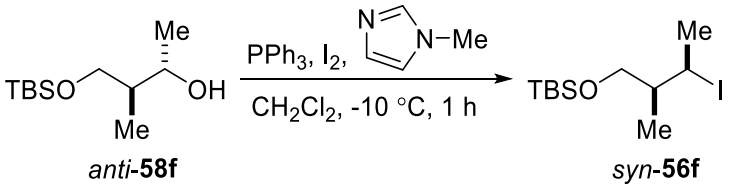
^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.63 (qd, *J* = 7.2, 2.4 Hz, 1H), 3.48 (dd, *J* = 9.9, 4.5 Hz, 1H), 3.32 – 3.26 (m, 1H), 1.93 (d, *J* = 7.2 Hz, 3H), 0.87 (m, 13H), 0.07 (d, *J* = 5.7 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 68.3, 43.3, 37.8, 26.9, 26.1, 18.4, 14.1, -5.1, -5.2.

MS (70 eV, EI) *m/z* (%): 271 (70) $[M\text{-}C_4H_9]^{+\bullet}$**,** 229 (10)**,** 215 (41), 155 (2), 143 (30), 99 (8), 97 (16), 85 (24), 77 (56), 57 (57), 44 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2956 (w), 2929 (w), 2895 (w), 2857 (w), 1471 (w), 1464 (w), 1444 (w), 1388 (w), 1377 (w), 1361 (w), 1334 (w), 1251 (m), 1188 (w), 1136 (m), 1093 (s), 1044 (w), 1019 (w), 1006 (w), 963 (w), 939 (w), 914 (w), 834 (vs), 814 (m), 774 (s), 667 (m).

HRMS (EI) *m/z*: calcd for $\mathbf{C_7H_{16}IOSi^{+\bullet}}$ $[M\text{-}C_4H_9]^{+\bullet}$: 271.0010, found 270.9881.



anti-**58f** *syn*-**56f**

syn-**56f**

According to the procedure for *anti*-**56a**, *anti*-**58f** (0.60 g, 2.7 mmol, dr=99:1) was used as a starting material. The crude product was purified by chromatography on silica gel with ^{i}hexane to afford *syn*-**56f** (0.21 g, 23% yield, dr=5:95) as pale pink oil with traces of elimination product.

^{1}H NMR (400 MHz, $CDCl_3$) δ: 4.45 (qd, *J* = 7.1, 4.9 Hz, 1H), 3.59 (dd, *J* = 10.1, 6.4 Hz, 1H), 3.48 (dd, *J* = 10.1, 5.7 Hz, 1H), 1.87 (d, *J* = 7.1 Hz, 3H), 1.85 – 1.77 (m, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.05 (d, *J* = 3.0 Hz, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) δ: 67.0, 44.7, 34.5, 26.1, 26.0, 24.9, 18.4, 15.0, -5.2, -5.3.

MS (70 eV, EI) *m/z* (%): 271 (97) $[M\text{-}C_4H_9]^{+\bullet}$**,** 229 (18)**,** 215 (100), 201 (10), 185 (91), 159 (4), 143 (30), 115 (12), 89 (14), 75 (38), 69 (64), 57 (54).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2955 (w), 2929 (w), 2857 (w), 1472 (w), 1463 (w), 1445 (w), 1387 (w), 1361 (w), 1253 (m), 1179 (w), 1127 (m), 1105 (m), 1088 (s), 1063 (m), 1042 (m), 1006 (w), 954 (w), 939 (w), 834 (vs), 814 (m), 773 (s), 667 (m).

HRMS (EI) *m/z*: calcd for $\mathbf{C_{10}H_{22}IOSi^{+\bullet}}$ $[M\text{-}CH_3]^{+\bullet}$: 313.0479, found 313.0485.

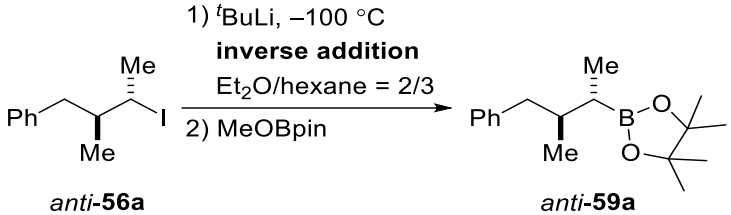
I/Li-exchange and following reactions

[General procedure A]

A dry and Ar-flushed *Schlenk*-tube was cooled to –100 °C and charged with a solution of ^{t}BuLi (0.40 mL, 1.88 M in pentane, 0.75 mmol) in mixture of Et_2O (1.5 mL) and ^{n}hexane (2.3 mL). A solution of alkyl iodide (0.30 mmol) in Et_2O (0.6 mL) was added dropwise for 5 min. After stirring for 5 sec, electrophile was added and the reaction mixture was stirred for 15 min at –100 °C. The reaction mixture was quenched with 7 drops of sat. aq. NH_4Cl solution and after an addition of $MgSO_4$ this mixture was passed through a pad of silica gel with EtOAc or Et_2O. The solvents were evaporated and the crude product was purified by column chromatography.

To determine the thermodynamic preferences of some organolithium species we have performed the following experiments:

A dry and Ar-flushed *Schlenk*-tube was cooled down to –100 °C and charged with a solution of ^{t}BuLi (0.40 mL, 1.88 M in pentane, 0.75 mmol) in mixture of Et_2O (1.5 mL) and ^{n}hexane (2.3 mL). A solution of alkyl iodide (0.30 mmol) in Et_2O (0.6 mL) was added dropwise for 5 min. After stirring for 10 sec, the reaction mixture was warmed to –50 °C and stirred for 30 min at –50 °C. The electrophile was added and the reaction mixture was stirred for 15 min at –50 °C. The reaction mixture was quenched with 7 drops of sat. aq. NH_4Cl solution and after an addition of $MgSO_4$ this mixture was passed through a pad of silica gel with EtOAc or Et_2O. Solvents were evaporated and the diastereomeric ratio was determined with ^{13}C-NMR of the crude product or after purification.



anti-**56a** *anti*-**59a**

anti-**59a**

According to **general procedure A**, *anti*-**56a** (82 mg, 0.30 mmol, dr=99:1) as a starting material material and MeOBpin (0.10 mL, 0.60 mmol) as an electrophile were used. The crude

product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/100 to afford *anti*-**59a** (68 mg, 83% yield, dr=99:1) as a colorless oil.

The thermodynamic equilibration experiment showed a diastereomeric ratio of the *anti*-**59a** to *syn*-**59a** of 66:34 compared to 99:1 (kinetic quenching).

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.30 – 7.22 (m, 2H), 7.19 – 7.13 (m, 3H), 2.81 (dd, *J* = 13.2, 5.3 Hz, 1H), 2.41 (dd, *J* = 13.2, 9.2 Hz, 1H), 2.02 (dq, *J* = 9.2, 5.9 Hz, 1H), 1.33 (s, 12H), 1.18 – 1.03 (m, 4H), 0.90 (d, *J* = 6.8 Hz, 3H).

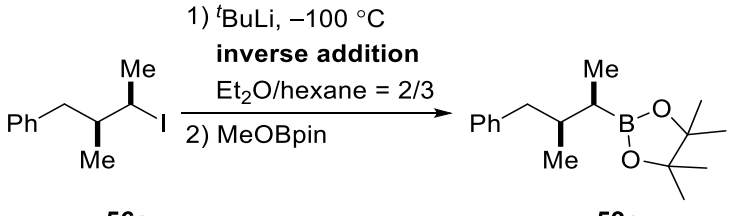
^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 142.2, 129.4, 128.1, 125.6, 83.0, 42.3, 38.3, 25.1, 24.9, 18.3, 13.3.

^{11}B-NMR (128 MHz, $CDCl_3$) *δ*: 29.3**.**

MS (70 eV, EI) *m/z* (%): 274 (1) $[M]^{+\bullet}$, 259 (3), 217 (1), 201 (2), 183 (42), 146 (6), 139 (40), 118 (10), 101 (72), 91 (50), 83 (100), 69 (36), 57 (72).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2977 (m), 2929 (w), 2873 (w), 1495 (w), 1454 (m), 1401 (w), 1387 (m), 1379 (m), 1370 (s), 1311 (s), 1271 (w), 1259 (w), 1215 (m), 1197 (w), 1165 (m), 1143 (vs), 1111 (m), 1071 (w), 1057 (w), 1042 (w), 1031 (w), 1011 (w), 966 (m), 865 (m), 845 (m), 738 (s), 698 (vs), 670 (w).

HRMS (EI) *m/z*: calcd for **$C_{17}H_{27}O_2B^{+\bullet}$** $[M]^{+\bullet}$: 274.2104, found 274.2084.



syn-**56a** *syn*-**59a**

syn-**59a**

According to general procedure, *syn*-**56a** (82 mg, 0.30 mmol, dr=5:95) as a starting material and MeOBpin (0.10 mL, 0.60 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/100 to afford *syn*-**59a** (49 mg, 60% yield, dr=6:94) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.38 – 7.31 (m, 2H), 7.28 – 7.21 (m, 3H), 2.80-2.69 (m, 2H), 2.53-2.43 (m, 2H), 2.06-1.98 (m, 1H), 1.33 (s, 12H), 1.18 – 1.03 (m, 4H), 0.90 (d, *J* = 6.8 Hz, 3H).

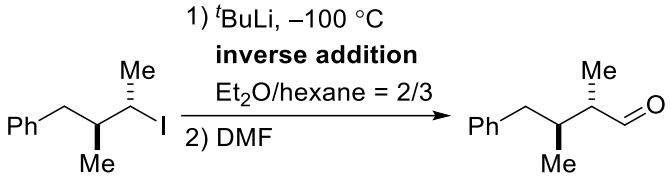
^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 142.1, 129.3, 128.2, 125.6, 83.0, 42.6, 37.2, 25.0, 24.9, 17.5, 11.2.

^{11}B-NMR (128 MHz, $CDCl_3$) *δ*: 29.3**.**

MS (70 eV, EI) *m/z* (%): 274 (8) $[M]^{+\bullet}$, 259 (11), 183 (100), 146 (9), 139 (75), 118 (15), 101 (94), 91 (82), 83 (94), 69 (33), 57 (44).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2996 (w), 2975 (w), 2958 (m), 2934 (m), 2875 (w), 1495 (w), 1491 (w), 1454 (m), 1401 (m), 1390 (m), 1380 (m), 1368 (s), 1349 (m), 1337 (m), 1311 (vs), 1289 (m), 1268 (m), 1212 (m), 1167 (m), 1144 (s), 1113 (m), 1098 (s), 1056 (w), 1022 (m), 986 (w), 975 (w), 964 (m), 952 (w), 875 (m), 846 (s), 831 (w), 778 (w), 741 (s), 718 (w), 701 (vs), 670 (m).

HRMS (EI) *m/z*: calcd for **$C_{17}H_{27}O_2B^{+\bullet}$** $[M]^{+\bullet}$: 274.2104, found 274.2096.



anti-**56a** *anti*-**59b**

anti-**59b**

According to general procedure, *anti*-**56a** (82 mg, 0.30 mmol, dr=99:1) as a starting material and DMF (0.06 mL, 0.75 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/15 to afford *anti*-**59b** (32 mg, 60% yield, dr=95:5) as a colorless oil.

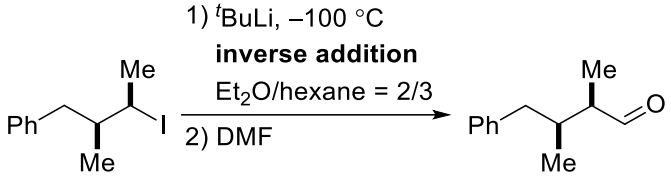
^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 9.69 (d, *J* = 1.8 Hz, 1H), 7.36 – 7.08 (m, 5H), 2.72 (dd, *J* = 13.4, 5.5 Hz, 1H), 2.44 – 2.31 (m, 2H), 2.28 – 2.17 (m, 1H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 205.4, 140.4, 129.3, 128.5, 126.3, 50.9, 39.8, 36.6, 17.2, 10.3.

MS (70 eV, EI) *m/z* (%): 176 (1) $[M]^{+\bullet}$, 159 (2), 143 (4), 118 (100), 91 (43), 65 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3027 (w), 2965 (w), 2876 (w), 1722 (s), 1603 (w), 1495 (w), 1454 (m), 1398 (w), 1381 (w), 1182 (w), 1156 (w), 1077 (w), 1030 (w), 1019 (w), 1004 (w), 975 (w), 912 (w), 892 (w), 855 (w), 825 (w), 736 (s), 699 (vs).

HRMS (EI) *m/z*: calcd for **$C_{12}H_{16}O^{+\bullet}$** $[M]^{+\bullet}$: 176.1201, found 176.1199.



syn-**56a** *syn*-**59b**

syn-**59b**

According to general procedure, *syn*-**56a** (82 mg, 0.30 mmol, dr=1:99) as a starting material and DMF (0.06 mL, 0.75 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/15 to afford *syn*-**59b** (36 mg, 70% yield, dr=7:93) as a colorless oil.

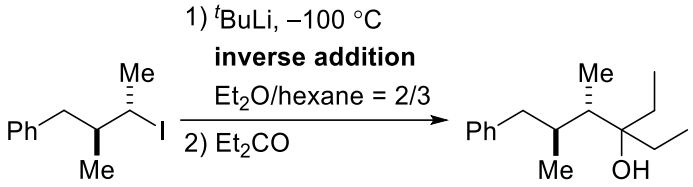
^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 9.63 (d, *J* = 1.1 Hz, 1H), 7.33 – 7.27 (m, 2H), 7.24 – 7.16 (m, 3H), 2.69 – 2.53 (m, 2H), 2.46 – 2.27 (m, 2H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 205.5, 140.4, 129.2, 128.6, 126.3, 49.6, 41.2, 34.8, 15.5, 7.9

MS (70 eV, EI) *m/z* (%): 176 (1) $[M]^{+\bullet}$, 143 (3), 118 (100), 105 (2), 91 (58), 77 (3) 65 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3028 (w), 2965 (w), 2930 (w), 2876 (w), 1721 (s), 1604 (vw), 1495 (w), 1454 (m), 1398 (w), 1382 (w), 1253 (w), 1181 (w), 1118 (w), 1068 (w), 1060 (w), 1030 (w), 1009 (w), 990 (w), 912 (w), 870 (w), 854 (w), 760 (w), 736 (s), 699 (vs), 649 (w), 621 (w), 596 (w).

HRMS (EI) *m/z*: calcd for **$C_{12}H_{16}O^{+\bullet}$** $[M]^{+\bullet}$: 176.1201, found 176.1194.



anti-**56a** *anti*-**59c**

anti-**59c**

According to general procedure, *anti*-**56a** (85 mg, 0.31 mmol, dr=99:1) as a starting material and Et_2CO (0.06 mL, 0.6 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with EtOAc/^{i}hexane = 1/10 to afford *anti*-**59c** (52 mg, 71% yield, dr=97:3) as a colorless oil.

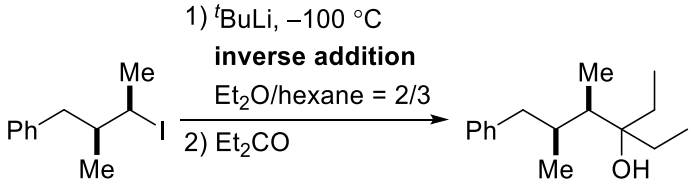
^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.28 – 7.24 (m, 2H), 7.20 – 7.14 (m, 3H), 3.16 (d, *J* = 12.6 Hz, 1H), 2.21 – 2.03 (m, 2H), 1.80 – 1.47 (m, 5H), 1.35 – 1.20 (m, 1H), 0.96 (d, *J* = 7.2 Hz, 3H), 0.92-0.84 (m, 6H), 0.83 (d, *J* = 6.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 143.0, 129.2, 128.2, 125.6, 77.6, 43.6, 38.3, 34.3, 29.4, 28.5, 20.1, 8.2, 8.1

MS (70 eV, EI) *m/z* (%): 205 (12) $[M- C_2H_5]^{+\bullet}$, 187 (2), 145 (14), 118 (79), 91 (68), 87 (100), 69 (21), 45 (30).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3493 (vw), 3026 (w), 2966 (m), 2882 (w), 1603 (w), 1496 (w), 1454 (m), 1380 (m), 1322 (w), 1260 (w), 1154 (m), 1074 (w), 1031 (w), 1017 (w), 985 (w), 943 (s), 924 (m), 871 (w), 826 (w), 762 (w), 739 (s), 698 (vs).

HRMS (EI) *m/z*: calcd for **$C_{14}H_{21}O^{+\bullet}$** $[M-C_2H_5]^{+\bullet}$: 205.1592, found 205.1606.



syn-**56a** *syn*-**59c**

syn-**59c**

According to general procedure, *syn*-**56a** (80 mg, 0.29 mmol, dr=2:98) as a starting material and Et_2CO (0.06 mL, 0.6 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with EtOAc/^{i}hexane = 1/10 to afford *syn*-**59c** (34 mg, 50% yield, dr=8:92) as a colorless oil.

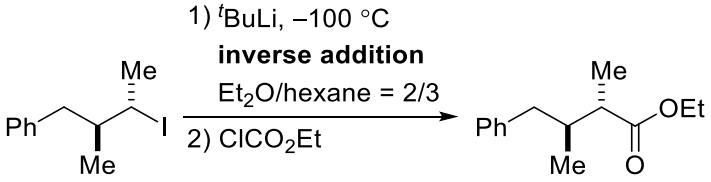
^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.30 – 7.23 (m, 2H), 7.21 – 7.13 (m, 3H), 2.58 – 2.45 (m, 2H), 2.23 – 2.12 (m, 1H), 1.60 – 1.45 (m, 3H), 1.45 – 1.34 (m, 2H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 7.2 Hz, 3H), 0.74 (t, *J* = 7.5 Hz, 3H), 0.68 (t, *J* = 7.5 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 141.8, 129.3, 128.3, 125.9, 77.3, 44.0, 40.1, 34.1, 28.9, 28.1, 15.9, 7.8, 7.8, 7.7.

MS (70 eV, EI) *m/z* (%): 205 (12) $[M- C_2H_5]^{+\bullet}$, 187 (2), 145 (12), 118 (74), 91 (63), 87 (100), 69 (16), 57 (18), 45 (29).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3495 (vw), 3026 (w), 2966 (m), 2938 (m), 2881 (w), 1603 (vw), 1496 (w), 1453 (m), 1383 (w), 1324 (w), 1258 (w), 1151 (w), 1117 (w), 1090 (w), 1068 (w), 1030 (w), 1013 (w), 983 (w), 944 (s), 925 (m), 899 (w), 829 (vw), 809 (w), 759 (w), 740 (s), 699 (vs).

HRMS (EI) *m/z*: calcd for **$C_{14}H_{21}O^{+\bullet}$** $[M-C_2H_5]^{+\bullet}$: 205.1592, found 205.1596.



anti-**56a** *anti*-**57a**

anti-**57a**

According to general procedure, *anti*-**56a** (82 mg, 0.30 mmol, dr=99:1) as a starting material and $ClCO_2Et$ (0.06 mL, 0.6 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/50 to afford *anti*-**57a** (55 mg, 82% yield, d.r.=97:3) as a colorless oil.

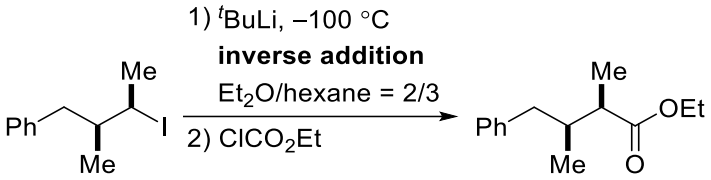
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.28 (m, 2H), 7.23 – 7.14 (m, 3H), 4.24 – 4.08 (m, 2H), 2.83 (dd, *J* = 13.3, 5.1 Hz, 1H), 2.48 – 2.38 (m, 1H), 2.32 (dd, *J* = 13.3, 9.5 Hz, 1H), 2.12 – 2.00 (m, 1H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.19 (d, *J* = 7.0 Hz, 3H), 0.86 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ: 175.9, 141.0, 129.3, 128.3, 126.0, 60.2, 44.3, 40.1, 38.5, 16.8, 14.5, 14.2.

MS (70 eV, EI) *m/z* (%): 220 (3) $[M]^{+\bullet}$, 175 (6), 147 (4), 118 (21), 102 (100), 91 (70), 74 (45), 65 (12), 56 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2972 (w), 1729 (vs), 1496 (w), 1454 (m), 1379 (m), 1298 (w), 1249 (m), 1179 (s), 1153 (s), 1114 (m), 1095 (m), 1075 (m), 1060 (m), 1029 (m), 970 (m), 911 (w), 894 (w), 859 (m), 791 (w), 761 (m), 738 (s), 699 (vs).

HRMS (EI) *m/z*: calcd for **$C_{14}H_{20}O_2^{+\bullet}$** $[M]^{+\bullet}$: 220.1463, found 220.1451.



syn-**56a** *syn*-**57a**

syn-**57a**

According to general procedure, *syn*-**56a** (82 mg, 0.30 mmol, dr=5:95) as a starting material and $ClCO_2Et$ (0.06 mL, 0.6 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with EtOAc/^{i}hexane = 1/10 to afford *syn*-**57a** (50 mg, 75% yield, dr=9:91) as a colorless oil.

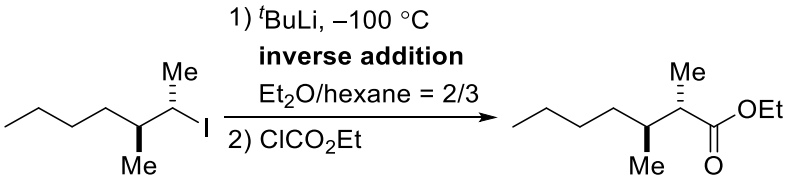
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.34 – 7.24 (m, 2H), 7.23 – 7.14 (m, 3H), 4.14 (qd, *J* = 7.1, 1.9 Hz, 2H), 2.69 (dd, *J* = 13.4, 5.6 Hz, 1H), 2.45 – 2.33 (m, 2H), 2.26 – 2.14 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H), 0.83 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 176.5, 140.8, 129.2, 128.4, 126.1, 60.3, 44.0, 41.3, 37.5, 15.6, 14.4, 12.6.

MS (70 eV, EI) *m/z* (%): 220 (3) $[M]^{+\bullet}$, 175 (6), 147 (3), 118 (14), 102 (100), 91 (56), 74 (47), 65 (12), 57 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2964 (w), 2927 (m), 1730 (vs), 1496 (w), 1454 (m), 1380 (m), 1372 (m), 1331 (w), 1314 (w), 1251 (m), 1179 (s), 1153 (s), 1114 (m), 1096 (m), 1071 (m), 1059 (m), 1030 (m), 860 (w), 794 (w), 761 (w), 737 (m), 699 (vs).

HRMS (EI) *m/z*: calcd for **$C_{14}H_{20}O_2^{+\bullet}$** $[M]^{+\bullet}$: 220.1463, found 220.1443.



anti-**56b** *anti*-**57b**

anti-**57b**

According to general procedure, *anti*-**56b** (72 mg, 0.30 mmol, dr=99:1) as a starting material and $ClCO_2Et$ (0.06 mL, 0.6 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{n}pentane = 1/30 to afford *anti*-**57b** (48 mg, 75% yield, dr=97:3) as a colorless oil.

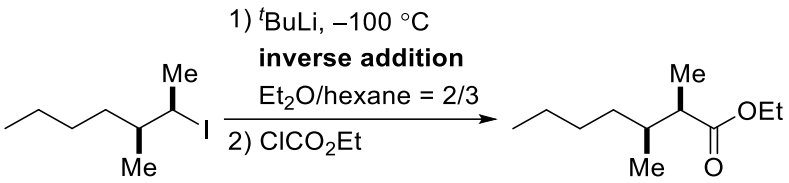
^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 4.20 – 4.04 (m, 2H), 2.32 (p, *J* = 6.9 Hz, 1H), 1.78 – 1.66 (m, 1H), 1.44 – 1.15 (m, 9H), 1.09 (d, *J* = 7.0 Hz, 3H), 0.89 (d, *J* = 6.6 Hz, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 176.5, 60.1, 44.9, 36.1, 33.1, 29.3, 23.0, 17.4, 14.5, 14.2, 14.0.

MS (70 eV, EI) *m/z* (%): 171 (4) $[M\text{-}CH_3]^{+\bullet}$, 141 (13), 129 (8), 102 (100), 74 (21), 57 (3).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2959 (m), 2928 (m), 2874 (m), 2859 (m), 1733 (vs), 1459 (m), 1378 (m), 1259 (m), 1214 (w), 1178 (s), 1144 (m), 1094 (m), 1048 (m), 1025 (m), 798 (m).

HRMS (EI) *m/z*: calcd for **$C_{11}H_{23}O_2^{+\bullet}$** $[M+H]^{+\bullet}$: 187.1698, found 187.1671.



syn-**56b** *syn*-**57b**

syn-**57b**

According to general procedure, *syn*-**56b** (72 mg, 0.30 mmol, dr=1:99) as a starting material and $ClCO_2Et$ (0.06 mL, 0.6 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{n}pentane = 1/30 to afford *syn*-**57b** (35 mg, 63% yield, dr=5:95) as a colorless oil.

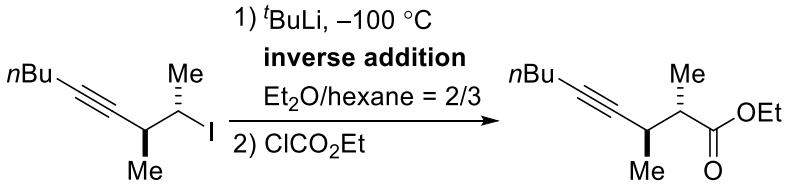
^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 4.21 – 4.04 (m, 2H), 2.35 (p, *J* = 6.8 Hz, 1H), 1.88 – 1.74 (m, 1H), 1.33 – 1.13 (m, 9H), 1.05 (d, *J* = 7.1 Hz, 3H), 0.92 – 0.81 (m, 6H)

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 176.8, 60.1, 44.4, 35.5, 34.6, 29.6, 23.0, 15.8, 14.4, 14.2, 12.4.

MS (70 eV, EI) *m/z* (%): 171 (1) $[M\text{-}CH_3]^{+\bullet}$, 141 (6), 129 (10), 102 (100), 74 (481), 57 (16).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2961 (w), 2930 (w), 2875 (vw), 2860 (vw), 1723 (m), 1459 (w), 1381 (w), 1260 (w), 1184 (w), 1096 (w), 1045 (w), 907 (s), 861 (vw), 797 (vw), 728 (vs).

HRMS (EI) *m/z*: calcd for **$C_{11}H_{23}O_2^{+\bullet}$** $[M+H]^{+\bullet}$: 187.1698, found 187.1692.



anti-**56c** *anti*-**57c**

anti-**57c**

According to general procedure, *anti*-**56c** (65 mg, 0.24 mmol, dr=99:1) as a starting material and $ClCO_2Et$ (0.05 mL, 0.5 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{n}pentane = 1/30 to afford *anti*-**57c** (37 mg, 72% yield, dr=97:3) as a colorless oil.

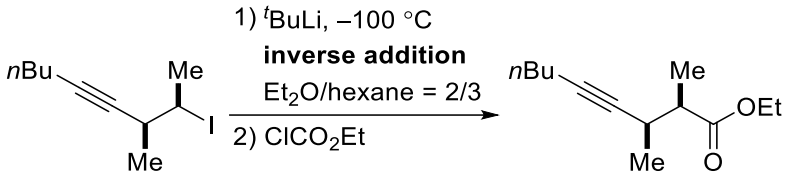
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.20 – 4.07 (m, 2H), 2.82 – 2.70 (m, 1H), 2.33 (p, *J* = 7.2 Hz, 1H), 2.19 – 2.09 (m, 2H), 1.50 – 1.32 (m, 4H), 1.28 – 1.22 (m, 6H), 1.13 (d, *J* = 6.9 Hz, 3H), 0.89 (t, *J* = 7.0 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ: 175.5, 82.3, 81.7, 60.5, 45.7, 31.3, 29.6, 22.0, 20.0, 18.5, 15.0, 14.4, 13.8.

MS (70 eV, EI) *m/z* (%): 195 (91) $[M\text{-}CH_3]^{+\bullet}$, 181 (18), 167 (100), 153 (6), 139 (13), 125 (7), 121 (8), 111 (19), 102 (7), 95 (37), 81 (22), 74 (9), 67 (25), 55 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2960 (m), 2934 (m), 2875 (w), 1734 (vs), 1458 (m), 1375 (m), 1345 (m), 1299 (w), 1257 (m), 1240 (w), 1173 (s), 1163 (s), 1127 (m), 1098 (m), 1073 (m), 1026 (m), 862 (w).

HRMS (EI) *m/z*: calcd for **$C_{13}H_{21}O_2^{+\bullet}$** $[M\text{-}H]^{+\bullet}$: 209.1542, found 209.1538.



syni-**56c** *syn*-**57c**

syn-**57c**

According to general procedure, *syn*-**56c** (79 mg, 0.29 mmol, dr=1:99) as a starting material and $ClCO_2Et$ (0.06 mL, 0.6 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/*n*pentane = 1/30 to afford *syn*-**57c** (38 mg, 61% yield, dr=1:99) as a colorless oil.

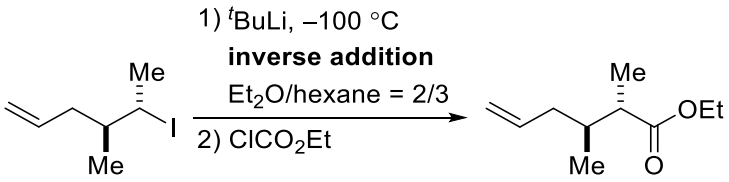
^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 4.14 (q, *J* = 7.1 Hz, 2H), 2.84 – 2.73 (m, 1H), 2.51 (p, *J* = 6.9 Hz, 1H), 2.18 – 2.06 (m, 2H), 1.49 – 1.32 (m, 4H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.17 (d, *J* = 6.9 Hz, 3H), 1.12 (d, *J* = 7.1 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 175.1, 82.5, 81.7, 60.4, 45.1, 31.3, 29.0, 22.0, 18.5, 17.7, 14.4, 13.8, 13.5.

MS (70 eV, EI) *m/z* (%): 195 (78) $[M\text{-}CH_3]^{+\bullet}$, 181 (58), 167 (100), 153 (11), 139 (30), 125 (8), 121 (10), 111 (20), 102 (13), 95 (46), 81 (30), 67 (42), 55 (19).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2977 (w), 2960 (w), 2934 (w), 2875 (w), 1734 (s), 1455 (w), 1378 (w), 1372 (w), 1344 (w), 1331 (w), 1288 (w), 1259 (m), 1187 (m), 1159 (m), 1136 (w), 1112 (m), 1098 (w), 1065 (m), 1025 (m), 913 (m), 862 (w), 802 (w), 760 (w), 732 (vs), 648 (w).

HRMS (EI) *m/z*: calcd for $C_{13}H_{22}O_2^{+\bullet}$ $[M]^{+\bullet}$: 210.1620, found 210.1608.



anti-**56d** *anti*-**57d**

anti-**57d**

According to general procedure, *anti*-**56d** (112 mg, 0.5 mmol, dr=97:3) as a starting material and $ClCO_2Et$ (0.1 mL, 1.0 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{n}pentane = 1/30 to afford *anti*-**57d** (54 mg, 64% yield, dr=96:4) as a colorless oil.

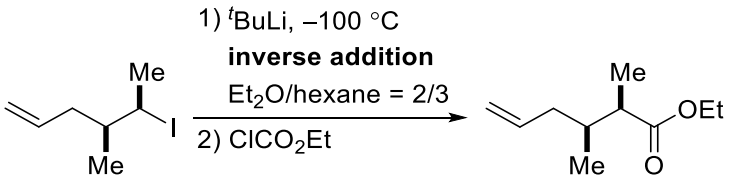
^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 5.82 – 5.67 (m, 1H), 5.09 – 4.94 (m, 2H), 4.21 – 4.04 (m, 2H), 2.35 (p, *J* = 7.0 Hz, 1H), 2.26 – 2.14 (m, 1H), 1.98 – 1.73 (m, 2H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 176.2, 136.8, 116.5, 60.2, 44.3, 38.0, 36.1, 17.2, 14.4, 14.3.

MS (70 eV, EI) *m/z* (%): 170 (8) $[M]^{+\bullet}$, 155 (78), 129 (7), 125 (32), 102 (100), 97 (15), 74 (19), 59 (7), 55 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2976 (w), 2935 (w), 2880 (w), 1731 (vs), 1456 (w), 1379 (m), 1299 (w), 1257 (m), 1228 (w), 1178 (s), 1140 (m), 1096 (m), 1077 (m), 1047 (m), 1027 (m), 994 (m), 912 (m), 860 (w).

HRMS (EI) *m/z*: calcd for **$C_{10}H_{18}O_2^{+\bullet}$** $[M]^{+\bullet}$: 170.1307, found 170.1306.



syn-**56d** *syn*-**57d**

syn-**57d**

According to general procedure, *syn*-**56d** (90 mg, 0.4 mmol, dr=5:95) as a starting material and $ClCO_2Et$ (0.08 mL, 0.8 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{n}pentane = 1/30 to afford *syn*-**57d** (47 mg, 69% yield, dr=9:91) as a colorless oil.

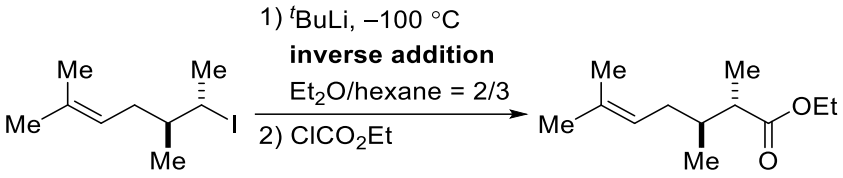
^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 5.84 – 5.67 (m, 1H), 5.08 – 4.95 (m, 2H), 4.20 – 4.06 (m, 2H), 2.38 (p, *J* = 6.9 Hz, 1H), 2.14 – 2.03 (m, 1H), 2.00 – 1.87 (m, 2H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.07 (d, *J* = 6.9 Hz, 3H), 0.85 (d, *J* = 6.2 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 176.6, 137.1, 116.4, 60.2, 43.8, 39.4, 35.3, 15.7, 14.4, 12.4.

MS (70 eV, EI) *m/z* (%): 170 (1) $[M]^{+\bullet}$, 155 (9), 125 (10), 102 (100), 97 (16), 74 (49), 69 (12), 55 (22).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2964 (m), 2926 (m), 1734 (vs), 1458 (m), 1260 (s), 1180 (s), 1154 (m), 1096 (s), 1073 (m), 1024 (s), 996 (m), 912 (m), 803 (s).

HRMS (EI) *m/z*: calcd for **$C_{10}H_{18}O_2^{+\bullet}$** $[M]^{+\bullet}$: 170.1307, found 170.1298.



anti-**65** *anti*-**66**

anti-**66**

According to general procedure, *anti*-**65** (75 mg, 0.3 mmol, dr=97:3) as a starting material and $ClCO_2Et$ (0.06 mL, 0.6 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/*n*pentane = 1/30 to afford *anti*-**66** (39 mg, 66% yield, dr=97:3) as a colorless oil.

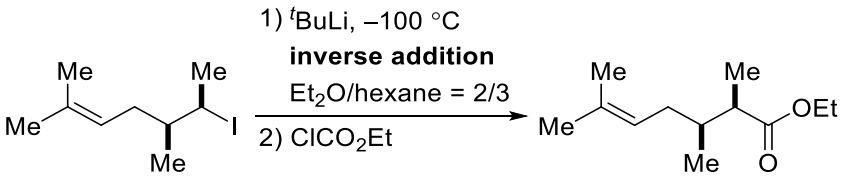
^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 5.15 – 5.04 (m, 1H), 4.12 (qd, *J* = 7.1, 3.3 Hz, 2H), 2.40 – 2.29 (m, 1H), 2.13 – 2.03 (m, 1H), 1.90 – 1.72 (m, 2H), 1.70 (s, 3H), 1.59 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.12 (d, *J* = 7.0 Hz, 3H), 0.88 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 176.4, 132.9, 122.6, 60.1, 44.4, 37.0, 32.0, 26.0, 26.0, 18.0, 17.3, 14.5, 14.3.

MS (70 eV, EI) *m/z* (%): 198 (15) $[M]^{+\bullet}$, 153 (13), 125 (4), 115 (3), 102 (100), 96 (44), 74 (44), 55 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980 (m), 2932 (v), 1722 (vs), 1465 (vw), 1456 (m), 1379 (s), 1346 (w), 1323 (w), 1299 (w), 1263 (w), 1232 (w), 1195 (w), 1182 (m), 1161 (w), 1095 (w), 1072 (w), 1034 (w), 986 (w).

HRMS (EI) *m/z*: calcd for **$C_{12}H_{22}O_2^{+\bullet}$** $[M]^{+\bullet}$: 198.1620, found 198.1623.



syn-**65** *syn*-**66**

syn-**66**

According to general procedure, *syn*-**65** (76 mg, 0.3 mmol, dr=1:99) as a starting material and $ClCO_2Et$ (0.06 mL, 0.6 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{n}pentane = 1/30 to afford *syn*-**66** (27 mg, 46% yield, dr=3:97) as a colorless oil.

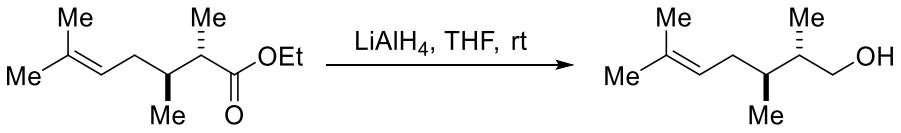
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.16 – 5.05 (m, 1H), 4.12 (qd, *J* = 7.1, 2.5 Hz, 2H), 2.42 – 2.29 (m, 1H), 2.05 – 1.79 (m, 3H), 1.70 (s, 3H), 1.59 (s, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 7.0 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ: 176.8, 132.9, 122.9, 60.2, 44.0, 36.3, 33.5, 26.0, 18.0, 15.8, 14.4, 12.6.

MS (70 eV, EI) *m/z* (%):198 (19) $[M]^{+\bullet}$, 153 (16), 125 (4), 115 (2), 102 (100), 96 (42), 74 (34), 69 (22), 55 (6).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2967 (m), 2928 (w), 2915 (w), 2877 (w), 1731 (vs), 1454 (m), 1378 (m), 1370 (m), 1349 (w), 1321 (w), 1251 (m), 1175 (s), 1153 (s), 1118 (m), 1096 (m), 1068 (m), 1036 (m), 860 (w), 846 (w).

HRMS (EI) *m/z*: calcd for **$C_{12}H_{22}O_2^{+\bullet}$** $[M]^{+\bullet}$: 198.1620, found 198.1609.



anti-**65** **62**

62 (±)-lasiol

A solution of *anti*-**66** (40.0 mg, 0.2 mmol) in THF (15 mL) was added dropwise to a suspension of $LiAlH_4$ (20.3 mg, 0.35 mmol) in THF (1 mL) at 0 °C. The reaction mixture was warmed up to room temperature and stirred overnight. The reaction mixture was cooled back to 0 °C and Na_2SO_4×10 H_2O was added until the suspension became white and no bubbling was observed. The residue was filtered off and washed with Et_2O. The resulted solution was evaporated and concentrated *in vacuo*. The crude product was purified by column

chromatography on silica gel with Et_2O/^{n}pentane = 1/4 to afford **62** (26.1 mg, 83% yield, dr=97:3) as a colorless oil. The relative configuration was determined by comparing with reported experimental values.[99]

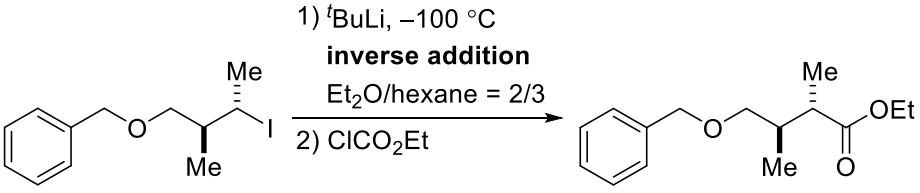
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.16 – 5.06 (m, 1H), 3.64 (dd, *J* = 10.5, 5.4 Hz, 1H), 3.46 (dd, *J* = 10.5, 7.1 Hz, 1H), 2.08 – 1.97 (m, 1H), 1.85 – 1.74 (m, 1H), 1.70 (s, 3H), 1.65 – 1.50 (m, 5H), 1.29 – 1.21 (m, 1H), 0.92 (d, *J* = 6.8 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ: 132.2, 123.7, 66.3, 40.4, 35.7, 31.6, 26.0, 18.0, 17.2, 14.0.

MS (70 eV, EI) *m/z* (%): 156 (16) $[M]^{+\bullet}$, 138 (10), 123 (30), 109 (19), 96 (27), 84 (29), 82 (25), 70 (67), 55 (54), 41 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3328 (w), 3324 (w), 2962 (s), 2925 (s), 2916 (s), 2875 (s), 1452 (s), 1376 (s), 1351 (w), 1232 (w), 1153 (w), 1119 (m), 1093 (m), 1076 (m), 1041 (vs), 1024 (vs), 985 (m), 931 (w), 868 (w), 840 (m), 774 (m), 699 (w), 694 (w), 690 (m), 685 (m), 682 (m), 678 (m), 668 (m), 658 (m), 654 (m).

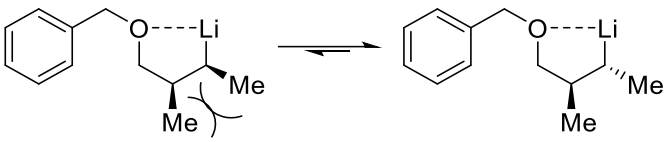
HRMS (EI) *m/z*: calcd for **$C_{10}H_{20}O^{+\bullet}$** $[M]^{+\bullet}$: 156.1509, found 156.1509.



anti-**56e** *anti*-**57e**

anti-**57e**

According to general procedure, *anti*-**56e** (91 mg, 0.3 mmol, dr=96:4) as a starting material and $ClCO_2Et$ (0.06 mL, 0.6 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/10 to afford *anti*-**57e** (58 mg, 77% yield, dr=91:9) as a colorless oil. The thermodynamic equilibration experiment ($ClCO_2Et$ was used as an electrophile) showed a diastereomeric ratio of the *anti*-**57e** to *syn*-**57e** of 34:66 compared to 91:9 (kinetic quenching). This observation could be explained by intramolecular coordination of lithium to oxygen.



anti-**55e** *syn*-**55e**

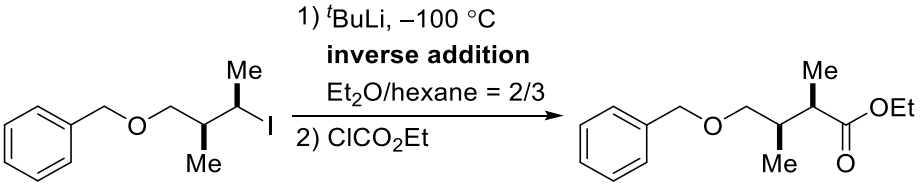
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.35 – 7.12 (m, 5H), 4.48 – 4.34 (m, 2H), 4.10 – 3.96 (m, 2H), 3.39 – 3.20 (m, 2H), 2.49 (p, *J* = 7.0 Hz, 1H), 2.08 – 1.91 (m, 1H), 1.16 (t, *J* = 7.0 Hz, 3H), 1.05 (d, *J* = 7.0 Hz, 3H), 0.90 (d, *J* = 7.0 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ: 176.0, 138.7, 128.4, 127.7, 127.6, 73.2, 73.0, 60.2, 41.8, 36.8, 15.1, 14.4, 14.3.

MS (70 eV, EI) *m/z* (%): 159 (4) $[M\text{-}C_7H_7]^{+\bullet}$, 143 (8), 113 (17), 102 (51), 91 (100), 74 (10), 55 (4).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2977 (w), 2879 (w), 1729 (vs), 1496 (w), 1454 (m), 1377 (m), 1306 (m), 1258 (m), 1181 (s), 1162 (s), 1137 (s), 1094 (vs), 1072 (vs), 1038 (s), 1028 (s), 920 (m), 860 (m), 807 (w), 796 (w), 737 (s), 715 (m), 697 (vs).

HRMS (EI) *m/z*: calcd for **$C_{15}H_{22}O_3^{+\bullet}$** $[M]^{+\bullet}$: 250.1569, found 250.1555.



syn-**56e** *syn*-**57e**

syn-**57e**

According to general procedure, *syn*-**56e** (125 mg of mixture (87 mg of pure), 0.29 mmol, dr=5:95) as a starting material and $ClCO_2Et$ (0.06 mL, 0.6 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{n}hexane = 1/10 to afford *syn*-**57e** (43 mg, 60% yield, dr=10:90) as a colorless oil.

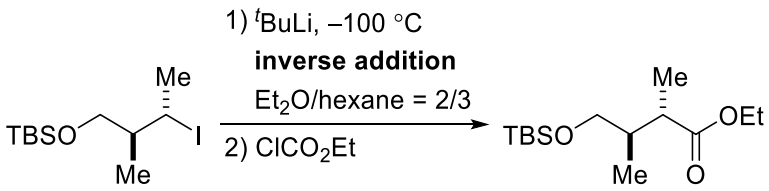
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.32 – 7.15 (m, 5H), 4.48 – 4.36 (m, 2H), 4.02 (q, *J* = 7.1 Hz, 2H), 3.28 – 3.22 (m, 2H), 2.56 – 2.46 (m, 1H), 2.19 (p, *J* = 6.8 Hz, 1H), 1.15 (t, *J* = 7.1 Hz, 3H), 1.00 (d, *J* = 7.1 Hz, 3H), 0.82 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ: 176.5, 138.6, 128.4, 127.7, 127.6, 73.6, 73.1, 60.3, 41.2, 35.6, 14.4, 13.4, 12.4.

MS (70 eV, EI) *m/z* (%): 159 (5) $[M\text{-}C_7H_7]^{+\bullet}$, 143 (9), 113 (21), 102 (46), 91 (100), 74 (11), 65 (8), 55 (4).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2978 (w), 2935 (w), 2879 (w), 1728 (vs), 1477 (w), 1454 (m), 1379 (m), 1367 (m), 1316 (w), 1254 (m), 1186 (s), 1160 (m), 1136 (s), 1094 (s), 1071 (s), 1038 (m), 1028 (s), 957 (w), 920 (w), 908 (w), 860 (m), 796 (w), 736 (s), 697 (vs).

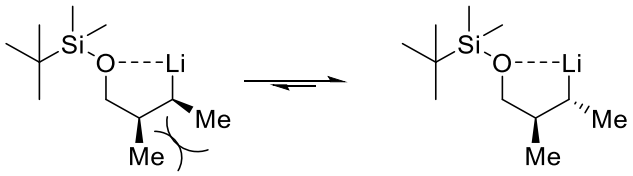
HRMS (EI) *m/z*: calcd for **$C_{15}H_{22}O_3^{+\bullet}$** $[M]^{+\bullet}$: 250.1569, found 250.1564.



anti-**56f** *anti*-**57f**

anti-**57f**

According to general procedure, *anti*-**56f** (98 mg, 0.3 mmol, dr=97:3) as a starting material and $ClCO_2Et$ (0.06 mL, 0.6 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/20 to afford *anti*-**56f** (60 mg, 72% yield, dr=94:6) as a colorless oil. The thermodynamic equilibration experiment ($ClCO_2Et$ was used as an electrophile) showed a diastereomeric ratio of the *anti*-**57f** to *syn*-**57f** of 15:85 compared to 94:6 (kinetic quenching). This observation could be explained by intramolecular coordination of lithium to oxygen.



anti-**55f** *syn*-**55f**

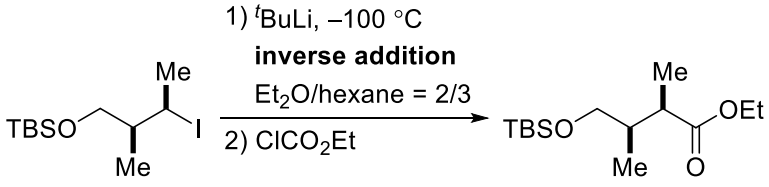
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.12 (q, *J* = 7.1Hz, 2H), 3.58 – 3.48 (m, 2H), 2.49 (p, *J* = 7.0 Hz, 1H), 1.92 – 1.80 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.9 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 6H)

^{13}C-NMR (101 MHz, $CDCl_3$) δ: 176.3, 65.4, 60.1, 41.5, 38.9, 26.0, 18.4, 14.9, 14.7, 14.4, -5.3.

MS (70 eV, EI) *m/z* (%): 259 (4) $[M\text{-}CH_3]^{+\bullet}$, 229 (16), 217 (65), 189 (15), 171 (5), 102 (23), 85 (33), 75 (100), 57 (64).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2957 (w), 2930 (m), 2858 (w), 1733 (s), 1472 (w), 1463 (w), 1389 (w), 1374 (w), 1362 (w), 1251 (m), 1179 (m), 1158 (m), 1135 (m), 1094 (s), 1075 (s), 1032 (m), 1006 (m), 974 (w), 939 (w), 835 (vs), 814 (m), 774 (s), 666 (m).

HRMS (EI) *m/z*: calcd for **$C_{13}H_{27}O_3Si^{+\bullet}$** $[M\text{-}CH_3]^{+\bullet}$: 259.1729, found 259.1711.



syn-**56f** *syn*-**57f**

syn-**57f**

According to general procedure, *syn*-**56f** (95 mg, 0.29 mmol, dr=5:95) as a starting material and $ClCO_2Et$ (0.06 mL, 0.6 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/10 to afford *syn*-**57f** (43 mg, 60% yield, dr=10:90) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.12 (q, *J* = 7.1 Hz, 2H), 3.44 (d, *J* = 6.7 Hz, 2H), 2.62 – 2.52 (m, 1H), 2.07 (hept, *J* = 6.7 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.06 (d, *J* = 7.1 Hz, 3H), 0.88 (s, 9H), 0.84 (d, *J* = 6.7 Hz, 3H), 0.03 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ: 176.7, 66.1, 60.2, 40.5, 37.8, 26.0, 18.4, 14.4, 12.8, 12.2, -5.3.

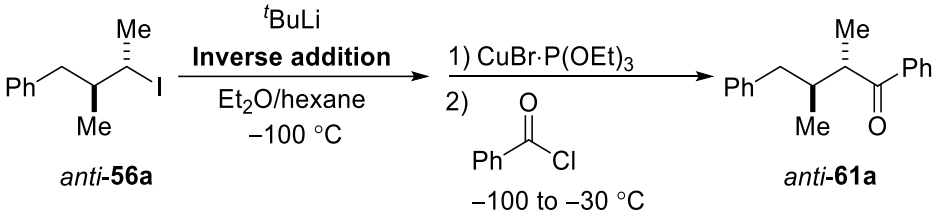
MS (70 eV, EI) *m/z* (%): 259 (4) $[M\text{-}CH_3]^{+\bullet}$, 229 (20), 217 (63), 189 (7), 171 (6), 127 (13), 57 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2957 (w), 2930 (m), 2858 (w), 1733 (s), 1472 (w), 1463 (w), 1389 (w), 1370 (w), 1362 (w), 1329 (w), 1314 (w), 1252 (m), 1185 (m), 1160 (m), 1134 (m), 1094 (s), 1069 (s), 1033 (m), 1006 (m), 966 (w), 939 (w), 923 (w), 835 (vs), 814 (m), 774 (s), 667 (m).

HRMS (EI) *m/z*: calcd for **$C_{13}H_{27}O_3Si^{+\bullet}$** $[M\text{-}CH_3]^{+\bullet}$: 259.1729, found 259.1747.

CuBr·P(OEt)$_3$ (CAS: 74540-61-7)

It was prepared according to literature.[122] The solutions were prepared under Ar in volumetric flasks to obtain 1M solution in Et_2O.



anti-**61a** (CAS: 920985-28-0)

A dry and Ar-flushed *Schlenk*-tube was cooled down to –100 °C and charged with a solution of ^{t}BuLi (0.35 mL, 2.15 M in pentane, 0.75 mmol) in mixture of Et_2O (1.3 mL) and ^{n}hexane (2.0 mL). A solution of *anti*-**56a** (82 mg, 0.30 mmol, dr=99:1) in Et_2O (0.6 mL) was added dropwise for 5 min. After stirring for 10 sec, a solution of CuBr·P(OEt)$_3$ (0.60 mL, 1 M in Et_2O, 0.60 mmol) was added and the reaction mixture was stirred for 10 min at –100 °C to observe the color change from yellow to green. Then benzoyl chloride (0.10 mL, 0.90 mmol) was added and the reaction mixture was gradually warmed up to –30 °C and stirred at for 18 h. After quenching the reaction mixture with aq. NH_3 solution, the reaction mixture was extracted with Et_2O (3×10 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The obtained crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/30 to afford *anti*-**61a** (47 mg, 62% yield, dr=96:4) as a colorless oil.

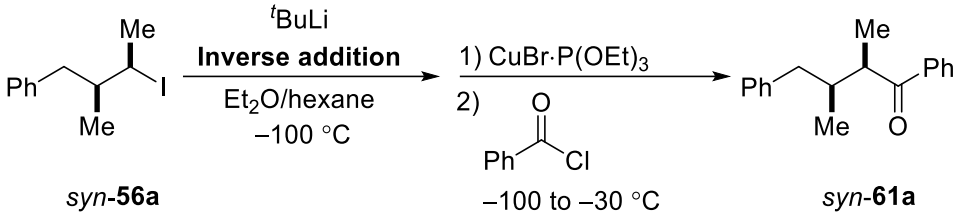
^{1}H-NMR (400 MHz, CDCl$_3$) *δ*: 7.93 (d, *J* = 7.1 Hz, 2H), 7.57 (t, *J* = 7.4 Hz, 1H), 7.48 (t, *J* = 7.4 Hz, 2H), 7.24 (t, *J* = 7.2 Hz, 2H), 7.17 (t, *J* = 7.3 Hz, 1H), 7.06 (d, *J* = 7.0 Hz, 2H), 3.52-3.43 (m, 1H), 2.93-2.81 (m, 1H), 2.32-2.18 (m, 2H), 1.28 (d, *J* = 6.9 Hz, 3H), 0.88 (d, *J* = 6.2 Hz, 3H).

^{13}C-NMR (100 MHz, CDCl$_3$) *δ*: 204.7, 140.9, 137.4, 132.9, 129.3, 128.8, 128.3, 128.3, 125.9, 45.9, 39.2, 38.0, 27.8, 13.8.

MS (70 eV, EI) *m/z* (%): 161 (1) $[M–C_7H_7]^{+\bullet}$, 134 (100), 105 (54), 89 (22), 77 (22), 51 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3062 (w), 3027 (w), 2965 (w), 2931 (w), 2874 (w), 1678 (m), 1596 (w), 1496 (w), 1448 (w), 1378 (w), 1260 (w), 1221 (w), 1182 (w), 1078 (w), 1030 (w), 1002 (w), 963 (w), 909 (w), 793 (w), 734 (m), 696 (vs), 658 (w).

HRMS (EI) *m/z*: calcd for **$C_{18}H_{20}O^{+\bullet}$** $[M]^{+\bullet}$: 252.1514, found 252.1506.



syn-**56a** *syn*-**61a**

syn-**61a**(CAS: 920985-27-9)

A dry and Ar-flushed *Schlenk*-tube was cooled down to –100 °C and charged with a solution of ^{t}BuLi (0.35 mL, 2.15 M in pentane, 0.75 mmol) in mixture of Et_2O (1.3 mL) and ^{n}hexane (2.0 mL). A solution of *syn*-**56a** (82 mg, 0.30 mmol, dr=2:98) in Et_2O (0.6 mL) was added dropwise for 5 min. After stirring for 10 sec, a solution of $CuBr{\cdot}P(OEt)_3$ (0.60 mL, 1 M in Et_2O, 0.60 mmol) was added and the reaction mixture was stirred for 10 min at –100 °C to observe the color change from yellow to green. Then benzoyl chloride (0.10 mL, 0.90 mmol) was added and the reaction mixture was gradually warmed up to –30 °C and stirred at for 18 h. After quenching the reaction mixture with aq. NH_3 solution, the reaction mixture was extracted with Et_2O (3×10 mL). The combined organic phase was dried over $MgSO_4$ and the solvents were evaporated. The obtained crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/30 to afford *syn*-**61a** (36 mg, 48% yield, dr=10:90) as a colorless oil.

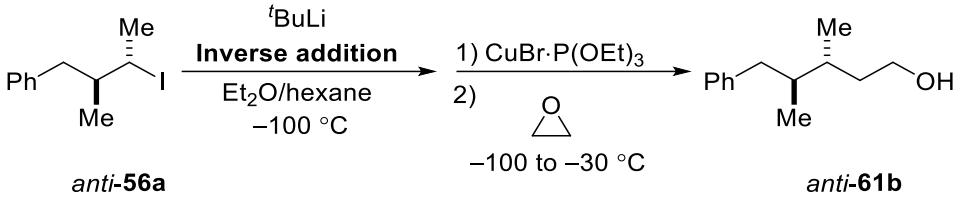
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.70 (d, *J* = 7.1 Hz, 2H), 7.51 (t, *J* = 7.4 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 2H), 7.33 (t, *J* = 7.3 Hz, 2H), 7.28-7.22 (m, 1H), 7.20 (d, *J* = 6.9 Hz, 2H), 3.40 (qd, *J* = 6.8, 4.9 Hz, 1H), 2.67 (d, *J* = 13.3, 7.6 Hz, 1H), 2.55 (d, *J* = 13.3, 7.2 Hz, 1H), 2.35-2.22 (m, 2H), 1.16 (d, *J* = 6.8 Hz, 3H), 0.85 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 204.7, 140.9, 137.4, 132.9, 129.3, 128.8, 128.3, 128.3, 125.9, 45.9, 39.2, 38.0, 27.8, 13.8.

MS (70 eV, EI) *m/z* (%): 161 (1) $[M–C_7H_7]^{+\bullet}$, 134 (100), 105 (57), 89 (22), 77 (23), 51 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3062 (w), 3027 (w), 2965 (w), 2931 (w), 2877 (w), 1678 (m), 1596 (w), 1495 (w), 1448 (w), 1381 (w), 1259 (w), 1221 (w), 1193 (w), 1180 (w), 1077 (w), 1030 (w), 1010 (w), 1002 (w), 969 (w), 957 (w), 909 (w), 791 (w), 734 (s), 693 (vs), 658 (w).

HRMS (EI) *m/z*: calcd for **$C_{18}H_{20}O^{+\bullet}$** $[M]^{+\bullet}$: 252.1514, found 252.1504.



anti-**61b**

A dry and Ar-flushed *Schlenk*-tube was cooled down to –100 °C and charged with a solution of ^{t}BuLi (0.35 mL, 2.15 M in pentane, 0.75 mmol) in mixture of Et_2O (1.3 mL) and ^{n}hexane (2.0 mL). A solution of *anti*-**56a** (82 mg, 0.30 mmol, dr=99:1) in Et_2O (0.6 mL) was added dropwise for 5 min. After stirring for 10 sec, a solution of $CuBr{\cdot}P(OEt)_3$ (0.60 mL, 1 M in Et_2O, 0.60 mmol) was added and the reaction mixture was stirred for 10 min at –100 °C to observe the color change from yellow to green. Then solution of ethylene oxide (0.30 mL, 2.5 M in THF, 0.75 mmol) was added and the reaction mixture was gradually warmed up to –30 °C and stirred at for 18 h. After quenching the reaction mixture with aq. NH_3 solution, the reaction mixture was extracted with Et_2O (3×10 mL). The combined organic phase was dried over $MgSO_4$ and solvents were evaporated. The obtained crude product was purified by column chromatography on silica gel with EtOAc/^{i}hexane = 1/5 to afford *anti*-**61b** (33 mg, 57% yield, dr=92:8) as a colorless oil.

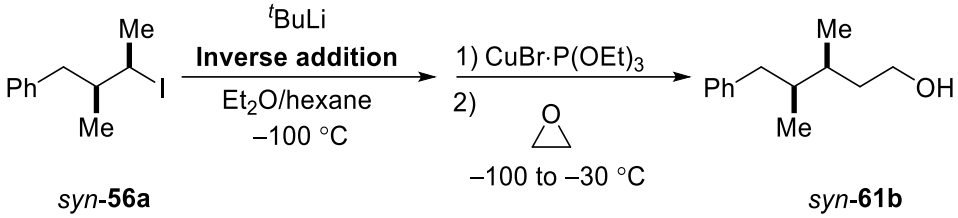
^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.30 – 7.25 (m, 2H), 7.21 – 7.13 (m, 3H), 3.79 – 3.71 (m, 1H), 3.71 – 3.61 (m, 1H), 2.71 (dd, *J* = 13.3, 5.2 Hz, 1H), 2.31 (dd, *J* = 13.3, 9.5 Hz, 1H), 1.83 – 1.68 (m, 2H), 1.67 – 1.56 (m, 1H), 1.55 – 1.34 (m, 2H), 0.93 (d, *J* = 6.8 Hz, 3H), 0.81 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 142.0, 129.2, 128.3, 125.8, 61.8, 40.3, 39.8, 35.8, 33.6, 16.9, 15.9.

MS (70 eV, EI) *m/z* (%): 192 (3) $[M]^{+\bullet}$, 174 (24), 145 (4), 117 (10), 104 (32), 91 (88), 83 (100), 77 (5), 65 (11), 55 (70).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3326 (w), 2957 (m), 2928 (m), 2874 (m), 1494 (w), 1453 (m), 1380 (m), 1259 (w), 1203 (w), 1180 (w), 1154 (w), 1082 (w), 1051 (m), 1030 (m), 1019 (m), 1002 (m), 909 (w), 843 (w), 734 (s), 698 (vs).

HRMS (EI) *m/z*: calcd for **$C_{13}H_{20}O^{+\bullet}$** $[M]^{+\bullet}$: 192.1509, found 192.1511.



syn-**56a** *syn*-**61b**

syn-**61b**

A dry and Ar-flushed *Schlenk*-tube was cooled down to –100 °C and charged with a solution of ^{t}BuLi (0.35 mL, 2.15 M in pentane, 0.75 mmol) in mixture of Et_2O (1.3 mL) and *n*-hexane (2.0 mL). A solution of *syn*-**56a** (82 mg, 0.30 mmol, dr=2:98) in Et_2O (0.6 mL) was added dropwise for 5 min. After stirring for 10 sec, a solution of $CuBr{\cdot}P(OEt)_3$ (0.60 mL, 1 M in Et_2O, 0.60 mmol) was added and the reaction mixture was stirred for 10 min at –100 °C to observe the color change from yellow to green. Then solution of ethylene oxide (0.30 mL, 2.5 M in THF, 0.75 mmol) was added and the reaction mixture was gradually warmed up to –30 °C and stirred at for 18 h. After quenching the reaction mixture with aq. NH_3 solution, the reaction mixture was extracted with Et_2O (3×10 mL). The combined organic phase was dried over $MgSO_4$ and solvents were evaporated. The obtained crude product was purified by column chromatography on silica gel with EtOAc/^{i}hexane = 1/5 to afford *syn*-**61b** (24 mg, 43% yield, dr=26:74) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.33 – 7.22 (m, 2H), 7.23 – 7.10 (m, 3H), 3.84 – 3.54 (m, 2H), 2.78 – 2.56 (m, 1H), 2.48 – 2.24 (m, 1H), 1.87 – 1.30 (m, 5H), 0.97 – 0.85 (m, 3H), 0.85 – 0.75 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ: 141.9, 129.2, 129.1, 128.3, 125.8, 61.6, 41.3, 39.4, 38.0, 32.8, 14.4, 14.2

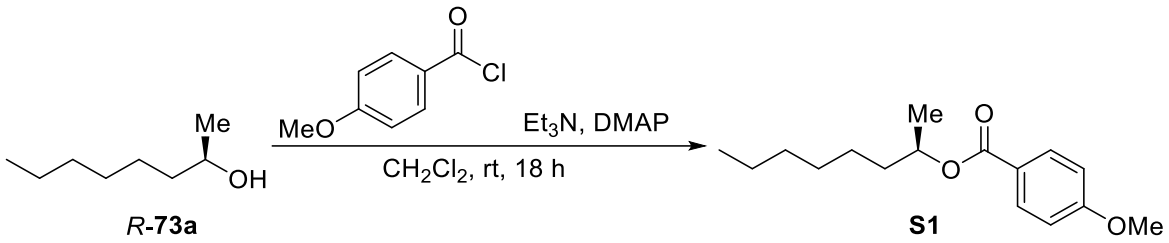
MS (70 eV, EI) *m/z* (%): 192 (2) $[M]^{+\bullet}$, 174 (25), 145 (4), 117 (10), 104 (37), 91 (97), 83 (100), 77 (5), 65 (11), 55 (75).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3326 (w), 2958 (m), 2927 (m), 2873 (w), 1494 (w), 1452 (m), 1380 (m), 1260 (w), 1111 (w), 1099 (w), 1052 (m), 1029 (m), 1002 (m), 909 (w), 797 (w), 732 (s), 697 (vs), 659 (w).

HRMS (EI) *m/z*: calcd for **$C_{13}H_{20}O^{+\bullet}$** $[M]^{+\bullet}$: 192.1509, found 192.1504.

Preparation of Optically Enriched Secondary Alkyllithium and Alkylcopper Reagents. Synthesis of (-)-Lardolure and Siphonarienal

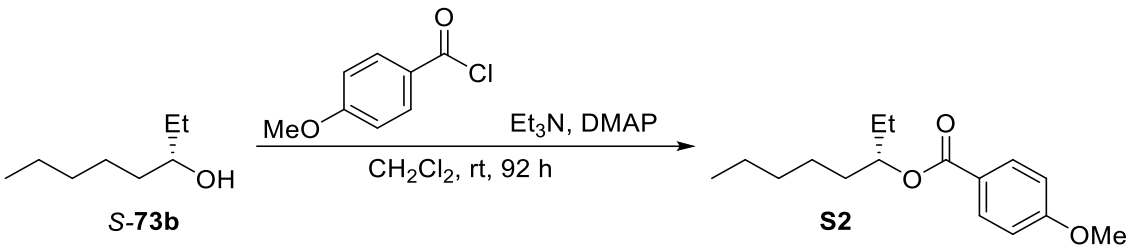
Determination of the *ee* of alcohols 73



S1 (CAS: 212687-56-4)

A flame-dried 25 mL flask was charged with a solution of DMAP (31.0 mg, 0.25 mmol), Et_3N (0.14 mL, 1.0 mmol) and alcohol *R*-**73a** (Fluka, 65.1 mg, 0.50 mmol) in CH_2Cl_2 (3 mL). 4-Methoxybenzoyl chloride (127.9 mg, 0.75 mmol) was added and the reaction mixture was stirred for 18 h at room temperature. The reaction mixture was quenched with sat. aq. $NaHCO_3$ solution and extracted with Et_2O (3×5 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/10 to afford **S1** (117.2 mg, 89% yield) as a colorless oil. The *ee* was determined on Daicel Chiralcel OB-H column with 2-propanol/heptane = 19/1, flow rate = 0.40 mL/min, temperature = 40 °C, wave length = 224 nm. Retention times: 10.6 min [major enantiomer], 11.6 min [minor enantiomer]. 96.0% *ee*.

The other analytical data is identical to reported one.[123]



S2

A flame-dried 25 mL flask was charged with a solution of DMAP (30.3 mg, 0.25 mmol), Et_3N (0.14 mL, 1.0 mmol) and alcohol *S*-**73b** (Aldrich, 65.0 mg, 0.50 mmol) in CH_2Cl_2 (3 mL). 4-Methoxybenzoyl chloride (128.1 mg, 0.75 mmol) was added and the reaction mixture was stirred for 92 h at room temperature. The reaction mixture was quenched with sat. aq. $NaHCO_3$ solution and extracted with Et_2O (3×5 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by column chromatography on silica gel with Et_2O/*i*hexane = 1/10 to afford **S2** (99.6 mg, 75% yield) as a colorless oil. The *ee* was determined on Daicel Chiralcel OD-H column with 2-propanol/heptane = 500/1, flow rate = 0.45 mL/min, temperature = 40 °C, wave length = 254 nm. Retention times: 19.3 min [minor enantiomer], 20.8 min [major enantiomer]. 95.4% *ee*.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 8.07 – 7.93 (m, 2H), 6.97 – 6.88 (m, 2H), 5.08 – 5.00 (m, 1H), 3.86 (s, 3H), 1.74 – 1.59 (m, 4H), 1.41 – 1.24 (m, 6H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.89 – 0.83 (m, 3H).

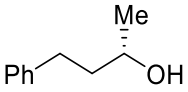
^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 166.3, 163.3, 131.7, 123.5, 113.7, 75.9, 55.6, 33.8, 31.9, 27.3, 25.2, 22.7, 14.2, 9.8.

MS (70 eV, EI) *m/z* (%): 264 (7) $[M]^{+\bullet}$, 152 (100), 135 (83), 107 (6), 92 (6), 77 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2957 (w), 2932 (w), 2859 (w), 1706 (m), 1605 (m), 1582 (w), 1510 (m), 1460 (w), 1420 (w), 1380 (w), 1357 (w), 1314 (w), 1301 (w), 1272 (m), 1251 (vs), 1165 (s), 1099 (s), 1030 (m), 1009 (w), 974 (w), 922 (w), 885 (w), 846 (m), 769 (m), 726 (w), 695 (w).

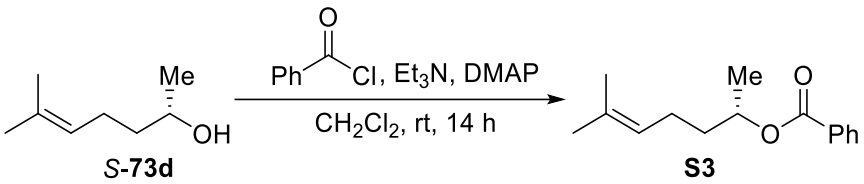
HRMS (EI) *m/z*: calcd for **$C_{16}H_{24}O_3^{+\bullet}$** $[M]^{+\bullet}$: 264.1725, found: 264.1722.

Optical rotation: $[\alpha]_D^{23}$= 13.3 (c 0.30, $CHCl_3$)



S-**73c** (CAS: 22148-86-3)

The *ee* was determined on Daicel Chiralcel OD-H column with 2-propanol/heptane = 10/1, flow rate = 0.50 mL/min, temperature = 40 °C, wave length = 224 nm. Retention times: 11.4 min [major enantiomer], 14.1 min [minor enantiomer]. 97.8% *ee*.



S-**73d** **S3**

S3

A flame-dried 10 mL flask was charged with a solution of DMAP (7.2 mg, 0.06 mmol), Et_3N (33.2 μL, 0.24 mmol) and alcohol *S*-**73d** (Alfa Aesar, 15.4 mg, 0.12 mmol) in CH_2Cl_2 (2 mL). Benzoyl chloride (20.9 μL, 0.18 mmol) was added and the reaction mixture was stirred for 14 h at room temperature. The reaction mixture was quenched with sat. aq. $NaHCO_3$ solution and extracted with Et_2O (3×5 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by column chromatography on silica gel with Et_2O/*n*hexane = 1/10 to afford **S3** (18.1 mg, 65% yield) as a colorless oil. The *ee* was determined on Daicel Chiralcel OB-H column with 2-propanol/heptane = 1000/1, flow rate = 0.30 mL/min, temperature = 40 °C, wave length = 245 nm. Retention times: 17.7 min [minor enantiomer], 19.9 min [major enantiomer]. 97.3% *ee*.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 8.08 – 8.02 (m, 2H), 7.58 – 7.51 (m, 1H), 7.47 – 7.40 (m, 2H), 5.20 – 5.09 (m, 2H), 2.15 – 2.04 (m, 2H), 1.85 – 1.75 (m, 1H), 1.67 (s, 3H), 1.68 – 1.59 (m, 1H), 1.57 (s, 3H), 1.34 (d, *J* = 6.3 Hz, 3H).

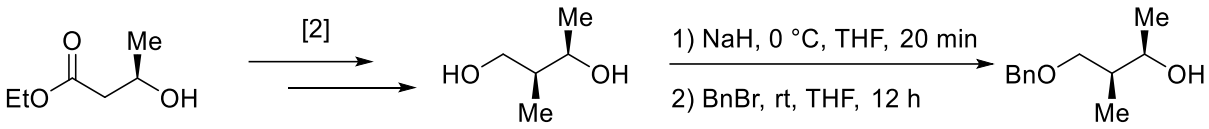
^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 166.4, 132.8, 132.3, 131.0, 129.6, 128.4, 123.6, 71.5, 36.2, 25.8, 24.2, 20.3, 17.8.

MS (70 eV, EI) *m/z* (%): 111 (58) $[M–PhCO_2]^{+\bullet}$, 95 (100), 77 (28), 55 (15).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2973 (w), 2926 (w), 2856 (w), 1715 (m), 1602 (w), 1584 (w), 1450 (w), 1377 (w), 1354 (w), 1313 (w), 1272 (s), 1175 (w), 1110 (m), 1067 (m), 1026 (w), 983 (w), 922 (w), 849 (w), 805 (w), 755 (w), 709 (vs), 687 (w), 672 (w).

HRMS (EI) *m/z*: calcd for **$C_8H_{15}^{+\bullet}$** $[M-PhCO_2]^{+\bullet}$: 111.1174, found: 110.0980.

Optical rotation: $[\alpha]_D^{23}$= 44.4 (c 0.09, $CHCl_3$), lit.[124] for *S*-enantiomer $[\alpha]_D^{20}$= -46.5 (c 0.8, $CHCl_3$).



S4 **S5** **S6**

S6

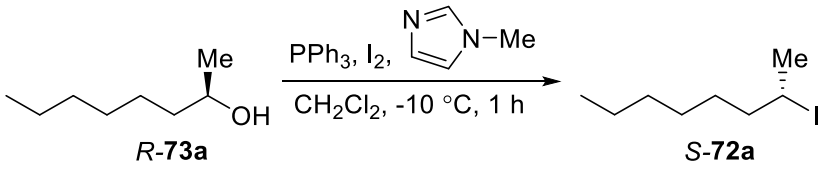
The diol **S5** was converted into the alcohol **S6** to determine the *ee* of the diol **S5**, which was used as a starting material for compound **S4**. The diol **S5** was obtained from commercially available alcohol **S4**, according to the literature.[125]

To a suspension of NaH (0.26 g, 60 wt% in mineral oil, 6.50 mmol) in THF (20 mL) a solution of diol **S5** (0.72 g, 6.85 mmol) in THF (5 mL) at 0 °C. The resulting reaction mixture was stirred at 0 °C for 20 min. Then benzyl bromide (0.81 ml, 6.85 mmol) was added the mixture was stirred for 12 h at room temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution at 0 °C and extracted with Et_2O (3×100 mL). The combined organic phase was dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by column chromatography on silica gel with EtOAc/^{i}hexane = 1/5 to afford **S6** (0.60 mg, 45% yield, dr = 98:2, >99% *ee*) as a colorless oil. The *ee* was determined on Daicel Chiralcel OD-H column with 2-propanol/heptane = 1/50, flow rate = 0.50 mL/min, temperature = 40 °C, wave length = 210 nm. Retention times: 21.1 min [major enantiomer]. >99% *ee*.

Other analytical data was identical to the literature values of the racemic compound.[125]

Optical rotation: $[\alpha]_D^{20}$= 17.4 (c 1.00, $CDCl_3$)

Starting material synthesis



R-**73a** *S*-**72a**

S-**72a** (CAS: 1809-04-7)

[Standard Procedure B]

To a solution of I_2 (1.65 g, 6.50 mmol) in CH_2Cl_2 (40 mL) PPh_3 (1.70 g, 6.50 mmol) was added in one portion at -10 °C and the resulting yellow suspension was stirred for 1 h at -10 °C. Then *N*-methylimidazole (0.51 mL, 6.50 mmol) was added. After 10 min of further stirring, a solution of alcohol *R*-**73a** (0.79 mL, 5.00 mmol, 96.0% *ee*) in CH_2Cl_2 (10 mL) was added and the reaction mixture was stirred for 1h at –10 °C. The reaction mixture was quenched with sat. aq. ($NaHSO_3$+$Na_2S_2O_5$) solution and extracted with CH_2Cl_2 (3×150 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated at 30 °C. The residue was triturated three times with ^{n}pentane. The precipitation was filtered off and all organic phases were combined. Solvents were evaporated at 30 °C. The crude product was purified by column chromatography on silica gel with ^{i}hexane to afford *S*-**72a** (0.89 g, 74% yield) as pale pink oil. The *ee* of *S*-**72a** was determined using GC with *Supelco β-DEX 120* column with 1.30 mL/min flow rate; temperature = 50 °C; average velocity = 40; 0.5 °C/min heating rate and holding time 20 min. Retention times: 29.41 min [minor enantiomer], 30.05 min [major enantiomer]. 90.0% *ee*.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 4.19 (dqd, *J* = 8.5, 6.8, 5.1 Hz, 1H), 1.92 (d, *J* = 6.8 Hz, 3H), 1.90 – 1.79 (m, 1H), 1.66 – 1.56 (m, 1H), 1.53 – 1.41 (m, 1H), 1.41 – 1.23 (m, 7H), 0.89 (t, *J* = 6.9 Hz, 3H).

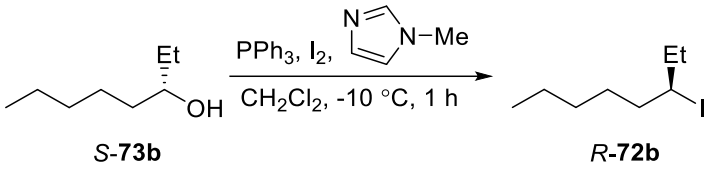
^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 43.1, 31.8, 31.1, 29.8, 29.1, 28.6, 22.7, 14.2.

MS (70 eV, EI) *m/z* (%): 240 (1) $[M]^{+\bullet}$, 205 (1), 113 (32), 83 (7), 71 (69), 57 (78), 43 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2965 (m), 2924 (vs), 2855 (m), 1455 (m), 1377 (m), 1296 (w), 1255 (w), 1227 (w), 1204 (w), 1165 (w), 1135 (s), 1057 (w), 992 (w), 877 (w), 805 (w), 723 (w).

HRMS (EI) *m/z*: calcd for **$C_8H_{17}I^{+\bullet}$** $[M]^{+\bullet}$: 240.0375, found: 240.0353.

Optical rotation: $[\alpha]_D^{23}$= 40.7 (c 0.27, $CHCl_3$), lit.[126] $[\alpha]_D^{20}$= 43.6 (neat)



S-**73b** *R*-**72b**

R-**72b**

The iodide *R*-**72b** was prepared according to **Standard Procedure B**, and alcohol *S*-**73b** (0.64 mL, 5.00 mmol, 95.5% *ee*) was used as a starting material. The crude product was purified by chromatography on silica gel with *i*-hexane to afford *R*-**72b** (0.65 g, 54% yield) as pale pink oil.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 4.09 (tt, *J* = 8.2, 4.7 Hz, 1H), 1.93 – 1.73 (m, 3H), 1.72 – 1.63 (m, 1H), 1.58 – 1.47 (m, 1H), 1.45 – 1.21 (m, 5H), 1.02 (t, *J* = 7.2 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H).

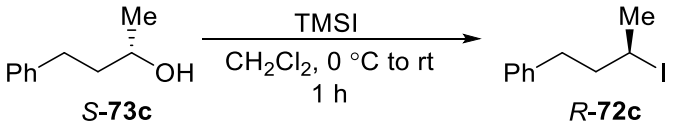
^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 43.0, 40.4, 33.9, 31.2, 29.4, 22.7, 14.3, 14.2.

MS (70 eV, EI) *m/z* (%): 240 (1) $[M]^{+\bullet}$, 113 (92), 71 (42), 57 (27), 55 (43), 43 (62), 41 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958 (s), 2928 (s), 2872 (m), 2857 (m), 2363 (w), 1456 (s), 1434 (w), 1379 (w), 1342 (w), 1284 (w), 1228 (w), 1204 (w), 1165 (w), 1129 (w), 1080 (w), 950 (w), 873 (w), 843 (w), 788 (w), 725 (w).

HRMS (EI) *m/z*: calcd for **$C_8H_{17}I^{+\bullet}$** $[M]^{+\bullet}$: 240.0369, found: 240.0355.

Optical rotation: $[\alpha]_D^{23}$= –23.4 (c 0.27, $CHCl_3$)



S-**73c** *R*-**72c**

R-**72c** (CAS: 1338073-50-9)

To a solution of alcohol *S*-**73c** (68.1 mg, 0.45 mmol, 97.8% *ee*) in CH_2Cl_2 (5 mL) TMSI (70 μL, 0.50 mmol) was added at 0 °C and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was quenched with sat. aq. $Na_2S_2O_3$ solution and extracted with CH_2Cl_2 (3×5 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated at 30 °C. The crude product was purified by column chromatography on silica gel with ^{i}hexane to afford *R*-**73c** (44.5 mg, 38% yield) as a colorless oil. The *ee* was determined on Daicel Chiralcel OB-H column with 2-propanol/heptane = 500/1, flow rate = 0.30 mL/min, temperature = 40 °C, wave length = 254 nm. Retention times: 22.4 min [major enantiomer], 25.9 min [minor enantiomer]. 95.4% *ee*.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.33 – 7.27 (m, 2H), 7.24 – 7.19 (m, 3H), 4.12 (dqd, *J* = 9.0, 6.8, 4.5 Hz, 1H), 2.85 (ddd, *J* = 13.9, 9.0, 5.2 Hz, 1H), 2.70 (ddd, *J* = 13.9, 9.0, 6.9 Hz, 1H), 2.16 (dtd, *J* = 14.5, 9.0, 5.2 Hz, 1H), 1.95 (d, *J* = 6.8 Hz, 3H), 1.88 (dddd, *J* = 14.5, 9.0, 7.0, 4.5 Hz, 1H).

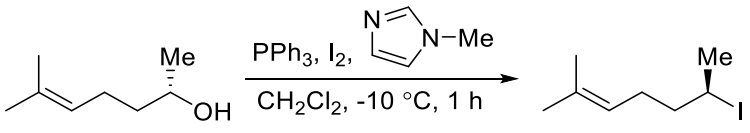
^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 140.9, 128.7, 128.6, 126.3, 44.5, 36.0, 29.9, 29.1.

MS (70 eV, EI) *m/z* (%): 240 (10) $[M]^{+\bullet}$, 133 (43), 91 (100), 65 (11).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3061 (w), 3025 (w), 2916 (w), 2858 (w), 1602 (w), 1494 (w), 1452 (w), 1376 (w), 1246 (w), 1205 (w), 1187 (w), 1134 (w), 1113 (w), 1084 (w), 1061 (w), 1030 (w), 993 (w), 913 (w), 812 (w), 763 (w), 745 (m), 696 (s), 606 (w).

HRMS (EI) *m/z*: calcd for **$C_{10}H_{13}I^{+\bullet}$** $[M]^{+\bullet}$: 260.0062, found: 260.0069.

Optical rotation: $[\alpha]_D^{23}$= -72.8 (c 0.14, $CHCl_3$),), lit.[127] $[\alpha]_D^{20}$= -80.0 (c 2.7, $CHCl_3$)



S-**73d** *R*-**72d**

R-**72d**

The iodide *R*-**72d** was prepared according to **Standard Procedure B**, and alcohol *S*-**73d** (200 mg, 1.56 mmol, 97.2% *ee*, Alfa Aesar) was used as a starting material. The crude product was

purified by column chromatography on silica gel with ^{n}pentane to afford *R*-**72d** (264 mg, 71% yield) as pale pink oil.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 5.07 (ddq, *J* = 8.5, 7.1, 1.3 Hz, 1H), 4.18 (dqd, *J* = 8.8, 6.8, 4.8 Hz, 1H), 2.22 – 2.02 (m, 2H), 1.93 (d, *J* = 6.8 Hz, 3H), 1.91 – 1.84 (m, 1H), 1.69 (d, *J* = 1.3 Hz, 3H), 1.65 (s, 3H), 1.64 – 1.56 (m, 1H).

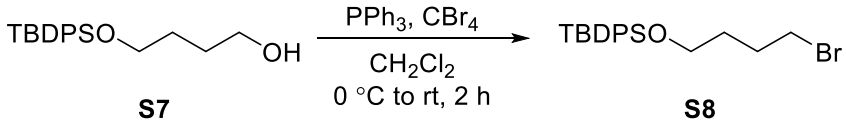
^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 133.1, 122.7, 43.1, 30.6, 29.1, 28.4, 25.9, 18.1.

MS (70 eV, EI) *m/z* (%): 238 (41) $[M]^{+\bullet}$, 127 (6), 111 (21), 95 (7), 69 (100), 57 (7).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2964 (m), 2914 (s), 1442 (s), 1376 (s), 1292 (w), 1230 (w), 1180 (s), 1141 (m), 1113 (m), 1079 (w), 984 (w), 901 (w), 843 (w), 824 (w), 744 (w).

HRMS (EI) *m/z*: calcd for **$C_8H_{15}I^{+\bullet}$** $[M]^{+\bullet}$: 238.0218, found: 238.0200.

Optical rotation: $[\alpha]_D^{23}$= –123.9 (c 0.14, $CHCl_3$)



S7 **S8**

S8 (CAS: 125010-58-4)

To a solution of alcohol **S7** (4.90 g, 15.0 mmol) and CBr_4 (6.00 g, 18.0 mmol) in CH_2Cl_2 (60 mL) PPh_3 (4.70 g, 18.00 mmol) was added in four portions at 0 °C. The reaction mixture was stirred for 30 min at 0 °C and it was warmed to room temperature. After 2 h of stirring at room temperature, the reaction mixture was diluted with ^{i}hexane. The precipitation was filtered off and solvents were removed from the filtrate. The further resulting precipitate was filtered off and it was washed with Et_2O/^{i}hexane = 1/10. The filtrate was evauporated. The crude product was purified by column chromatography on silica gel with Et_2O/ ^{i}hexane = 70/1 to afford **S8** (5.60 g, 96% yield) as a colorless oil.

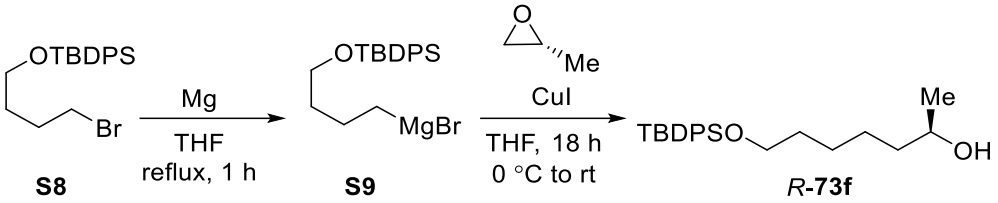
^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.69 – 7.62 (m, 4H), 7.47 – 7.35 (m, 6H), 3.69 (t, *J* = 6.1 Hz, 2H), 3.42 (t, *J* = 6.8 Hz, 2H), 2.06 – 1.93 (m, 2H), 1.77 – 1.64 (m, 2H), 1.05 (s, 9H).

^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 135.7, 133.9, 129.8, 127.8, 63.0, 34.1, 31.2, 29.6, 27.0, 19.4.

MS (70 eV, EI) *m/z* (%): 333 (20) [M–^{t}Bu]$^{+\bullet}$, 293 (40), 261 (100), 211 (32), 181 (23), 155 (5), 135 (5), 91 (7), 57 (6).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3070 (w), 2957 (w), 2931 (w), 2893 (w), 2857 (w), 1471 (w), 1462 (w), 1427 (w), 1389 (w), 1361 (w), 1249 (w), 1188 (w), 1104 (m), 1045 (w), 1006 (w), 997 (w), 961 (w), 939 (w), 822 (w), 793 (w), 739 (w), 725 (w), 699 (vs), 686 (w).

HRMS (EI) *m/z*: calcd for **$C_{16}H_{18}BrOSi^{+\bullet}$** [M–^{t}Bu]$^{+\bullet}$: 333.0310, found: 333.0271.



S8 **S9** ***R*-73f**

***R*-72f**

A flame-dried and Ar-flushed *Schlenk*-flask was charged with Mg turning (0.68 g, 28.0 mmol) and it was stirred overnight to activate it mechanically. THF (10 mL) and I_2 (ca. 5 mg) were added. The mixture was stirred and warmed gently with heat gun until the color of I_2 disappeared. Bromide **S8** (5.5 mL, 14.0 mmol) was added in such a rate to keep a mild reflux. After the addition, the reaction mixture was stirred for another 1 h at room temperature to obtain the desired Grignard reagent **S9** (79% yield, 0.65 M in THF).

To a solution of **S9** (10.8 mL, 0.65 M in THF, 7.00 mmol) CuI (130 mg, 0.70 mmol) was added in one portion at 0 °C and the resulted black suspension was stirred for 5 min at 0 °C. Then (*R*)-propylene oxide (0.49 mL, 7.00 mmol) in THF (10 mL) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and was stirred for 18 h at room temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution and extracted with Et_2O (3×100 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/1 to afford *R*-**73f** (2.40 g, 93% yield, >99% *ee*) as a colorless oil. The *ee* was estimated according to the *ee* of *R*-**73e**, obtained in the same way and from the same package of (*R*)-propylene oxide.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.69 – 7.64 (m, 4H), 7.45 – 7.35 (m, 6H), 3.83 – 3.72 (m, 1H), 3.66 (t, *J* = 6.4 Hz, 2H), 1.63 – 1.52 (m, 2H), 1.50 – 1.32 (m, 5H), 1.32 – 1.24 (m, 2H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.05 (s, 9H).

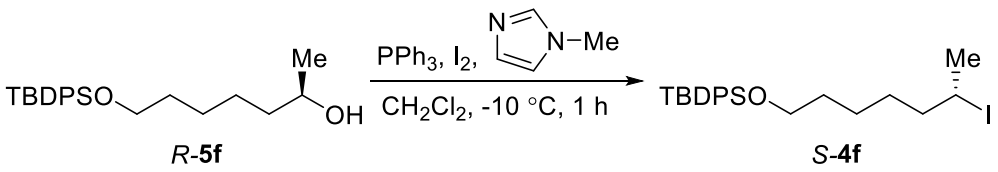
^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 135.7, 134.3, 129.6, 127.7, 68.3, 64.0, 39.5, 32.6, 27.0, 25.9, 25.6, 23.6, 19.4.

MS (70 eV, EI) *m/z* (%): 311 (11), 295 (6) [M–^{t}Bu–H_2O]$^{+\bullet}$, 217 (9), 199 (100), 181 (11), 163 (4), 139 (14), 123 (4), 97 (17), 55 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3347 (br s), 2959 (w), 2930 (w), 2857 (w), 1472 (w), 1462 (w), 1427 (w), 1389 (w), 1375 (w), 1361 (w), 1105 (m), 1092 (m), 1028 (w), 1007 (w), 998 (w), 938 (w), 822 (w), 799 (w), 738 (w), 699 (vs), 686 (m).

HRMS (EI) *m/z*: calcd for **$C_{23}H_{34}O_2Si^{+\bullet}$** [M–^{t}Bu]$^{+\bullet}$: 313.1624, found: 313.1646.

Optical rotation: $[\alpha]_D^{23}$= –5.9 (c 0.16, $CHCl_3$)



R-**5f** *S*-**4f**

S-**73f**

The iodide *S*-**73f** was prepared according to **Standard Procedure B**, and alcohol *R*-**72f** (1.11 g, 3.00 mmol, 99% *ee*) was used as a starting material. The crude product was purified by chromatography on silica gel with Et_2O/^{i}hexane = 1/100 to afford *S*-**73f** (1.12 g, 78% yield) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.72 – 7.65 (m, 4H), 7.48 – 7.36 (m, 6H), 4.17 (dqd, *J* = 8.5, 6.8, 5.0 Hz, 1H), 3.67 (t, *J* = 6.4 Hz, 2H), 1.92 (d, *J* = 6.8 Hz, 3H), 1.90 – 1.78 (m, 1H), 1.68 – 1.53 (m, 3H), 1.54 – 1.31 (m, 4H), 1.07 (s, 9H).

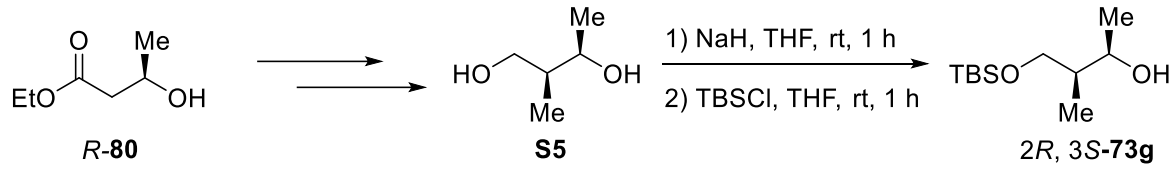
^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 135.7, 134.2, 129.7, 127.7, 63.9, 43.0, 32.5, 30.8, 29.6, 29.1, 27.0, 25.1, 19.4.

MS (70 eV, EI) *m/z* (%): 423 (40) [M–^{t}Bu]$^{+\bullet}$, 307 (97), 287 (36), 249 (26), 217 (14), 199 (100), 181 (47), 163 (7), 135 (12), 97 (77), 77 (7), 55 (31).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3070 (w), 2930 (w), 2856 (w), 1471 (w), 1461 (w), 1427 (w), 1388 (w), 1360 (w), 1188 (w), 1105 (m), 1092 (m), 1028 (w), 1006 (w), 997 (w), 938 (w), 822 (w), 801 (w), 738 (w), 699 (vs), 686 (w).

HRMS (EI) *m/z*: calcd for **$C_{23}H_{32}OISi^{+\bullet}$** [M–H]$^{+\bullet}$: 479.1267, found: 479.1248.

Optical rotation: $[\alpha]_D^{23}$= 24.8 (c 0.15, $CHCl_3$)

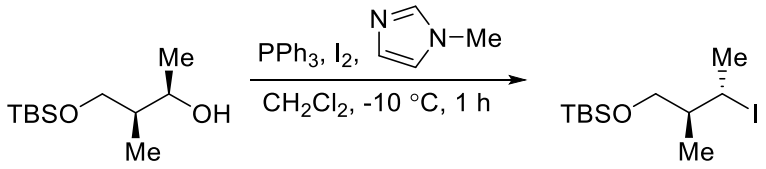


R-**80** **S5** 2*R*, 3*S*-**73g**

2*R*, 3*S*-**73g**

The diol **S5** was obtained from commercially available alcohol *R*-**80**, as was shown before. The compound 2*R*, 3*S*-**73g** (1.28 g, 86% yield, dr=98:2, >99% *ee*) was prepared from the diol **S5** (0.70 g, 6.80 mmol, dr=98:2, >99% *ee*). Other analytical data was identical to the values of the racemic compound.

Optical rotation: $[\alpha]_D^{21}$= 12.4 (c 1.06, $CDCl_3$)



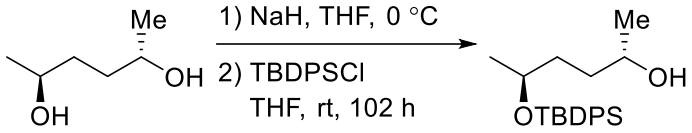
2*R*,3*S*-**73g** 2*S*,3*S*-**72g**

2*S*,3*S*-**72g**

The iodide 2*S*,3*S*-**72g** was prepared aw was mentioned before, and alcohol 2*R*, 3*S*-**73g** (1.05 g, 5.00 mmol, dr=98:2, >99% *ee*) was used as a starting material. The crude product was purified by column chromatography on silica gel with ^{t}hexane to afford 2*S*,3*S*-**72g** (0.88 g,

56% yield, dr=98:2, >99% *ee*) as pale pink oil. Other analytical data was identical to the literature values of the racemic compound.

Optical rotation: $[\alpha]_D^{22}$= 36.2 (c 1.0, $CDCl_3$)

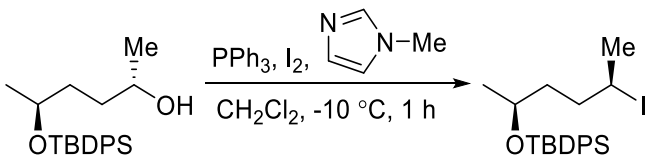


2*S*,5*S*-**73h**

2*S*,5*S*-**73h**

A flame-dried and N_2-flushed *Schlenk*-flask was charged with a suspension of NaH (0.21 g, 60 wt% in mineral oil, 5.30 mmol) and THF (10 mL) and the reaction mixture was cooled to 0 °C. A solution of (2*R*,4*R*)-2,4-pentanediol (TCI, 0.59 g, 5.00 mmol, dr=99:1, 99% *ee*) in THF (1 mL) was added and the resulting solution was stirred for 30 min at 0 °C to room temperature. Then *tert*-buthyldiphenylsilyl chloride (1.30 mL, 5.00 mmol) was added and the mixture was stirred for 102 h at room temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution at 0 °C and extracted with Et_2O (3×100 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/2 to afford 2*S*,5*S*-**73h** (1.48 g, 83% yield, dr=99:1, >99% *ee*) as a colorless oil. The *ee* was determined on Daicel Chiralcel OD-H column with 2-propanol/heptane = 1/200, flow rate = 0.30 mL/min, temperature = 40 °C, wave length = 230 nm. Retention times: 41.3 min [minor enantiomer], 44.5 min [major enantiomer]. >99% *ee*. Other analytical data was identical to the literature values of the racemic compound.[78]

Optical rotation: $[\alpha]_D^{23}$= –28.8 (c 0.13, $CHCl_3$)

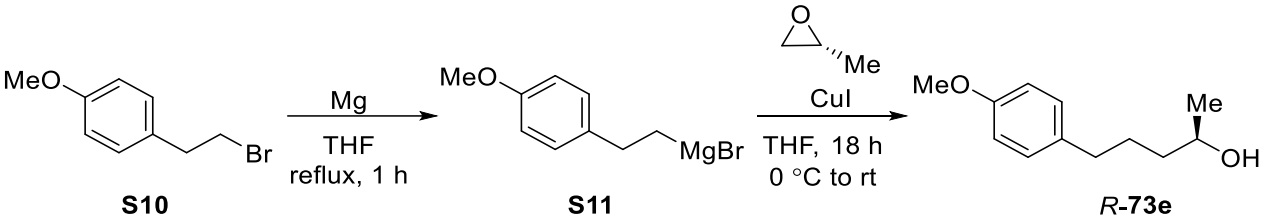


2S,5S-**73h** *2S,5R*-**72h**

2*S*,5*R*-**72h**

The iodide 2*S*,5*R*-**72h** was prepared according to **Standard Procedure B**, and alcohol 2*S*,5*S*-**73h** (1.10 g, 3.00 mmol, dr=99:1, 99% *ee*) was used as a starting material. The crude product was purified by chromatography on silica gel with Et_2O/hexane = 1/100 to afford 2*S*,5*R*-**73h** (1.21 g, 86% yield, dr = 99:1, >99% *ee*,) as a colorless oil. Other analytical data was identical to the literature values of the racemic compound.[78]

Optical rotation: $[\alpha]_D^{23}$= –59.3 (c 0.18, $CHCl_3$)



S10 **S11** ***R*-73e**

R-**73e**

A flame-dried and Ar-flushed *Schlenk*-flask was charged with Mg turning (1.37 g, 57.1 mmol) and it was stirred overnight to activate it mechanically. THF (25 mL) and I_2 (ca. 5 mg) were added. The mixture was stirred and warmed gently with heat gun until the color of I_2 disappeared. **S10** (6.10 g, 28.5 mmol, CAS: 14425-64-0) was added in such a rate to keep a mild reflux. After the addition, the reaction mixture was stirred for 1 h at room temperature to obtain the desired Grignard reagent **S11** (72% yield, 0.70 M in THF).

To a solution of **S11** (14.3 mL, 0.70 M in THF, 10.00 mmol) CuI (190 mg, 1.00 mmol) was added in one portion at 0 °C and the resulted black suspension was stirred for 5 min at 0 °C. Then (*R*)-propylene oxide (0.70 mL, 10.00 mmol) in THF (10 mL) was added dropwise at 0 °C. The reaction mixture was warmed to room temperature and was stirred for 18 h at room temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution and the reaction mixture extracted with Et_2O (3×100 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by chromatography on silica gel with Et_2O/hexane = 1/1 to afford *R*-**73e** (1.93 g, 99% yield, 99% *ee*) as a colorless oil. The *ee* was determined on Daicel Chiralcel OD-H column with 2-propanol/heptane = 1/20, flow rate = 0.50 mL/min, temperature = 30 °C, wave length = 230 nm. Retention times: 29.7 min [major enantiomer], 36.5 min [minor enantiomer]. >99% *ee*.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.13 – 7.07 (m, 2H), 6.87 – 6.79 (m, 2H), 3.86 – 3.75 (m, 1H), 3.79 (s, 3H), 2.58 (t, *J* = 7.6 Hz, 2H), 1.78 – 1.67 (m, 1H), 1.67 – 1.57 (m, 1H), 1.56 – 1.33 (m, 3H), 1.18 (d, *J* = 6.2 Hz, 3H).

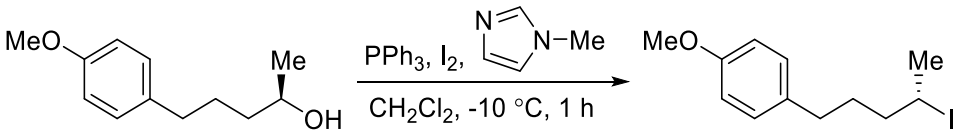
^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 157.8, 134.6, 129.4, 113.8, 68.2, 55.4, 38.9, 35.0, 28.0, 23.7.

MS (70 eV, EI) *m/z* (%): 194 (37) $[M]^{+\bullet}$, 161 (6), 134 (100), 121 (95), 91 (11), 79 (10).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3354 (br s), 2963 (w), 2932 (w), 2857 (w), 2835 (w), 1611 (w), 1583 (w), 1511 (s), 1462 (w), 1442 (w), 1373 (w), 1299 (w), 1242 (vs), 1176 (m), 1113 (w), 1089 (w), 1074 (w), 1034 (m), 1013 (w), 990 (w), 941 (w), 869 (w), 827 (m), 808 (m), 749 (w), 698 (w).

HRMS (EI) *m/z*: calcd for **$C_{12}H_{18}O_2^{+\bullet}$** $[M]^{+\bullet}$: 194.1307, found: 194.1297.

Optical rotation: $[\alpha]_D^{23}$= –19.2 (c 0.18, $CHCl_3$)



R-**73e** *S*-**72e**

S-**72e**

The iodide *S*-**72e** was prepared according to **Standard Procedure B**, and alcohol *R*-**73e** (0.97 g, 5.00 mmol, >99% *ee*) was used as a starting material. The crude product was purified by chromatography on silica gel with Et_2O/hexane = 1/15 to afford *S*-**72e** (1.31 g, 86% yield) as a colorless oil. The *ee* was determined on Daicel Chiralcel OD-H column with 2-propanol/heptane = 1/200, flow rate = 0.50 mL/min, temperature = 30 °C, wave length = 224 nm. Retention times: 21.6 min [major enantiomer], 23.1 min [minor enantiomer]. 98.9% *ee*.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.17 – 7.03 (m, 2H), 6.95 – 6.76 (m, 2H), 4.19 (dqd, *J* = 8.2, 6.8, 4.8 Hz, 1H), 3.79 (s, 3H), 2.66 – 2.51 (m, 2H), 1.91 (d, *J* = 6.8 Hz, 3H), 1.90 – 1.75 (m, 2H), 1.74 – 1.58 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 157.9, 134.1, 129.4, 113.9, 55.4, 42.4, 34.1, 31.9, 30.5, 29.1.

MS (70 eV, EI) *m/z* (%): 304 (40) $[M]^{+\bullet}$, 177 (13), 147 (3), 121 (100), 77 (6).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2980 (w), 2931 (w), 2856 (w), 2832 (w), 1611 (w), 1583 (w), 1510 (s), 1454 (w), 1441 (w), 1376 (w), 1300 (w), 1264 (w), 1243 (vs), 1199 (w), 1175 (m), 1133 (w), 1116 (w), 1035 (m), 986 (w), 955 (w), 900 (w), 827 (m), 807 (m), 774 (w), 748 (w), 733 (w), 711 (w), 698 (w).

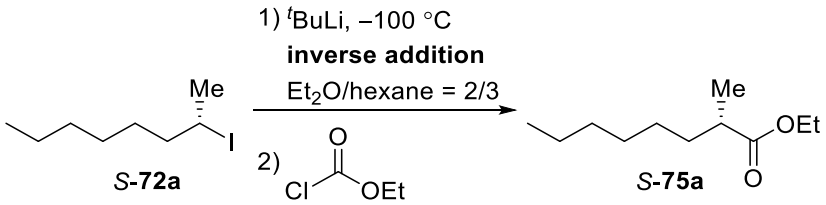
HRMS (EI) *m/z*: calcd for **$C_{12}H_{17}OI^{+\bullet}$** $[M]^{+\bullet}$: 304.0324, found: 304.0319.

Optical rotation: $[\alpha]_D^{23}$= 47.6 (c 0.14, $CHCl_3$)

I/Li-exchange and subsequent reactions

[Standard procedure C]

A flame-dried and Ar-flushed *Schlenk*-tube was cooled to –100 °C and charged with a solution of ^{t}BuLi (0.34 mL, 2.22 M in pentane, 0.75 mmol) in mixture of Et_2O (1.50 mL) and *n*-hexane (2.30 mL). A solution of alkyl iodide (0.30 mmol) in Et_2O (0.60 mL) was added dropwise in 1 min. After stirring for 10 sec, the electrophile (2.5 – 3 equiv.) was added and the reaction mixture was stirred for 5 min at –100 °C. The reaction mixture was quenched with 7 drops of sat. aq. NH_4Cl solution and after an addition of $MgSO_4$ this mixture was passed through a pad of silica gel with Et_2O. Solvents were evaporated and the crude product was purified by column chromatography.



S-**75a**

According to **Standard procedure C**, iodide *S*-**72a** (72.3 mg, 0.30 mmol) as a starting material and ethyl chloroformate (86 μL, 0.90 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/26 to afford *S*-**75a** (33.1 mg, 59% yield) as a colorless oil. The *ee* was determined by the further transformations described below.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.12 (q, *J* = 7.1 Hz, 2H), 2.40 (h, *J* = 7.0 Hz, 1H), 1.71 – 1.57 (m, 1H), 1.45 – 1.34 (m, 1H), 1.31 – 1.20 (m, 11H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.91 – 0.82 (m, 3H).

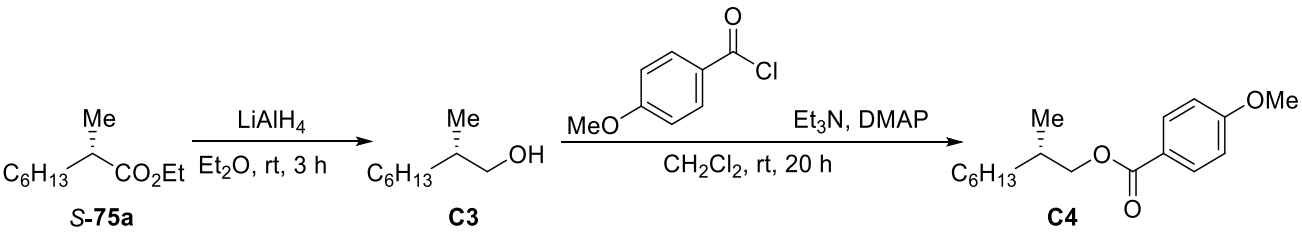
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 177.2, 60.2, 39.7, 34.0, 31.8, 29.3, 27.3, 22.7, 17.2, 14.4, 14.2.

MS (70 eV, EI) *m/z* (%): 186 (2) $[M]^{+\bullet}$, 157 (5), 141 (11), 102 (100), 74 (18), 57 (14).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2957 (w), 2928 (w), 2858 (w), 1733 (vs), 1463 (w), 1377 (w), 1349 (w), 1300 (w), 1250 (w), 1174 (m), 1146 (m), 1095 (w), 1027 (w), 859 (w), 763 (w), 725 (w).

HRMS (EI) *m/z*: calcd for **$C_{11}H_{22}O_2^{+\bullet}$** $[M]^{+\bullet}$: 186.1620, found: 186.1622.

Optical rotation: $[\alpha]_D^{23}$= 7.3 (c 0.28, $CHCl_3$)



S-**75a** **C3** **C4**

C4

A flame-dried 20 mL flask was charged with carboxylic ester *S*-**75a** (29.5 mg, 0.16 mmol) in Et_2O (1.5 mL). $LiAlH_4$ (15.0 mg, 0.40 mmol) was added and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was diluted with Et_2O and $Na_2SO_4 \cdot 10H_2O$ was added to quench it. The formed precipitate was filtered off and washed with Et_2O (3×3 mL). Solvents were evaporated from the filtrate to obtain the crude **C3**. A flame-dried 20 mL flask was charged with **C3** in CH_2Cl_2 (3 mL). Et_3N (44 μL, 0.32 mmol), DMAP (10.0 mg, 0.08 mmol) and 4-methoxybenzoyl chloride (33 μL, 0.24 mmol) were added successively, and the reaction mixture was stirred at room temperature for 20 h. The reaction mixture was quenched with the sat. aq. $NaHCO_3$ solution and extracted with Et_2O (3×10 mL). The combined organic phases were dried over $MgSO_4$ and solvents were evaporated. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/7 to afford **C4** (28.2 mg, 64% yield over 2 steps) as a colorless oil. The *ee* was determined on Daicel Chiralcel OB-

H column with 2-propanol/heptane = 1/100, flow rate = 0.30 mL/min, temperature = 40 °C, wave length = 254 nm. Retention times: 16.2 min [major enantiomer], 18.1 min [minor enantiomer]. 90.2% *ee*.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 8.05 – 7.95 (m, 2H), 6.96 – 6.88 (m, 2H), 4.17 (dd, J = 10.7, 5.8 Hz, 1H), 4.07 (dd, J = 10.7, 6.8 Hz, 1H), 3.86 (s, 3H), 1.98 – 1.84 (m, 1H), 1.51 – 1.17 (m, 10H), 1.00 (d, J = 6.7 Hz, 3H), 0.91 – 0.85 (m, 3H).

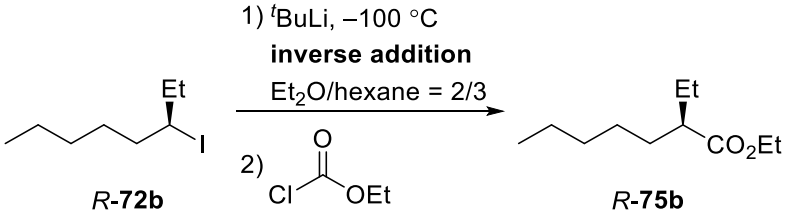
^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 166.6, 163.4, 131.7, 123.1, 113.7, 69.7, 55.5, 33.6, 32.9, 32.0, 29.7, 27.0, 22.8, 17.2, 14.2.

MS (70 eV, EI) *m/z* (%): 278 (2) $[M]^{+\bullet}$, 152 (100), 135 (59), 107 (4), 92 (4), 77 (6).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2957 (w), 2926 (w), 2855 (w), 1711 (m), 1606 (m), 1582 (w), 1511 (w), 1463 (w), 1420 (w), 1387 (w), 1377 (w), 1315 (w), 1272 (m), 1251 (vs), 1165 (s), 1112 (m), 1100 (m), 1030 (m), 1009 (w), 969 (w), 846 (m), 724 (w), 695 (w).

HRMS (EI) *m/z*: calcd for **$C_{17}H_{26}O_3^{+\bullet}$** $[M]^{+\bullet}$: 278.1882, found: 278.1875.

Optical rotation: $[\alpha]_D^{23}$= –6.0 (c 0.24, $CHCl_3$)



R-**75b**

According to **Standard procedure C**, iodide *R*-**72b** (72.0 mg, 0.30 mmol) as a starting material and ethyl chloroformate (86 μL, 0.90 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/26 to afford *R*-**75b** (30.4 mg, 54% yield) as a colorless oil. The *ee* was determined by the further transformations described below.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 4.14 (q, *J* = 7.1 Hz, 2H), 2.24 (tt, *J* = 8.8, 5.4 Hz, 1H), 1.68 – 1.38 (m, 4H), 1.35 – 1.19 (m, 9H), 0.92 – 0.83 (m, 6H).

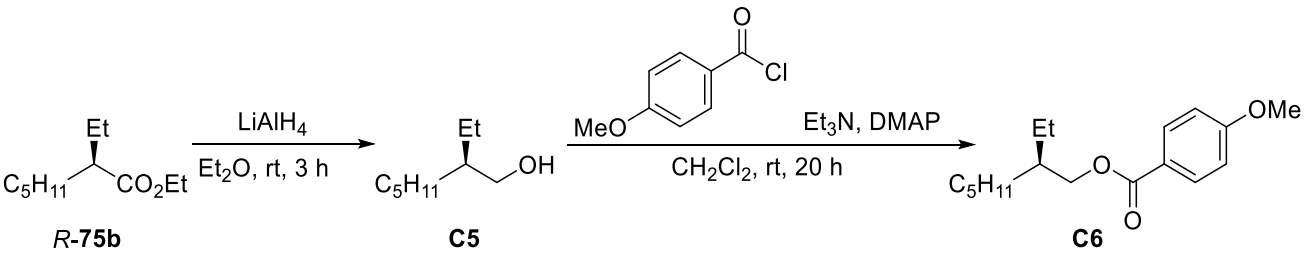
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 176.6, 60.1, 47.5, 32.2, 31.9, 27.2, 25.7, 22.6, 14.5, 14.2, 12.0.

MS (70 eV, EI) *m/z* (%): 186 (2) $[M]^{+\bullet}$, 171 (1), 158 (15), 141 (13), 129 (24), 116 (100), 101 (50), 88 (10), 73 (70), 57 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2960 (w), 2932 (w), 2874 (w), 2860 (w), 2361 (w), 1732 (vs), 1461 (w), 1377 (w), 1353 (w), 1300 (w), 1268 (w), 1240 (w), 1222 (w), 1174 (s), 1143 (m), 1121 (w), 1095 (w), 1028 (w), 1024 (w), 546 (w), 803 (w), 776 (w), 749 (w), 726 (w), 668 (w).

HRMS (EI) *m/z*: calcd for **$C_{11}H_{22}O_2^{+\bullet}$** $[M]^{+\bullet}$: 186.1620, found: 186.1622.

Optical rotation: $[\alpha]_D^{23}$= –12.3 (c 0.17, $CHCl_3$)



R-**75b** **C5** **C6**

C6

A flame-dried 20 mL flask was charged with carboxylic ester *R*-**9b** (18.5 mg, 0.10 mmol) in Et_2O (1 mL). $LiAlH_4$ (9.3 mg, 0.24 mmol) was added and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was diluted with Et_2O (3 mL) and $Na_2SO_4 \cdot 10H_2O$ was added for quenching. The formed precipitate was filtered off and washed with Et_2O. Solvents were evaporated from the filtrate to obtain the crude **C5**. A flame-dried 20 mL flask was charged with alcohol **C5** in CH_2Cl_2 (3 mL). Et_3N (25 μL, 0.18 mmol), DMAP (6.4 mg, 0.05 mmol) and 4-methoxybenzoyl chloride (18 μL, 0.14 mmol) were added successively, and the reaction mixture was stirred at room temperature for 20 h. The reaction mixture was quenched with the sat. aq. $NaHCO_3$ solution and extracted with Et_2O (3×10 mL). The combined organic phases were dried over $MgSO_4$ and solvents were evaporated. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/6

to afford **C6** (23.6 mg, 85% yield over 2 steps) as a colorless oil. The *ee* was determined on Daicel Chiralcel two OD-H columns with 2-propanol/heptane = 1/200, flow rate = 0.50 mL/min, temperature = 30 °C, wave length = 254 nm. Retention times: 36.0 min [major enantiomer], 37.8 min [major enantiomer]. 93.0% *ee*.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.04 – 7.95 (m, 2H), 6.96 – 6.88 (m, 2H), 4.25 – 4.16 (m, 2H), 3.86 (s, 3H), 1.78 – 1.64 (m, 1H), 1.50 – 1.22 (m, 10H), 0.94 (t, *J* = 7.5 Hz, 3H), 0.88 (t, *J* = 6.9 Hz, 3H).

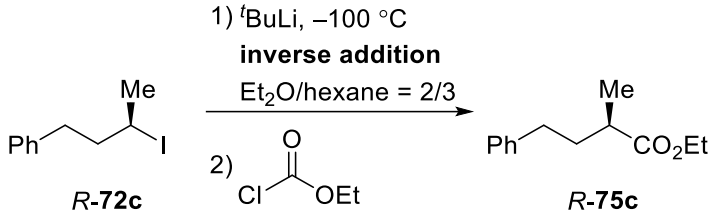
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.7, 163.4, 131.7, 123.2, 113.7, 67.2, 55.6, 39.1, 32.3, 31.0, 26.6, 24.2, 22.8, 14.2, 11.3.

MS (70 eV, EI) *m/z* (%): 278 (1) $[M]^{+\bullet}$, 152 (100), 135 (64), 97 (5), 91 (6), 85 (5), 83 (5), 77 (9), 70 (10), 57 (13), 43 (13).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3417 (w), 3079 (w), 2958 (w), 2928 (w), 2873 (w), 2858 (w), 2577 (w), 2357 (w), 2043 (w), 1910 (w), 1711 (m), 1606 (m), 1582 (w), 1511 (w), 1461 (w), 1420 (w), 1380 (w), 1315 (w), 1301 (w), 1272 (m), 1253 (s), 1180 (w), 1166 (m), 1112 (w), 1101 (m), 1031 (w), 1009 (w), 965 (w), 846 (w), 770 (w), 725 (w), 695 (w), 635 (w), 631 (w).

HRMS (EI) *m/z*: calcd for **$C_{17}H_{26}O_3^{+\bullet}$** $[M]^{+\bullet}$: 278.1876, found: 278.1872.

Optical rotation: $[\alpha]_D^{23}$= –12.8 (c 0.16 $CHCl_3$)



R-**75c**

According to **Standard procedure C**, iodide *R*-**72c** (40.2 mg, 0.15 mmol) as a starting material and ethyl chloroformate (43 μL, 0.45 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/27 to afford *R*-**75c** (18.1 mg, 59% yield) as a colorless oil. The *ee* was determined on Daicel Chiralcel OB-H column with 2-propanol/heptane = 1/9, flow rate = 0.75 mL/min, temperature = 30 °C, wave

length = 254 nm. Retention times: 12.1 min [major enantiomer], 14.9 min [minor enantiomer]. 90.2% *ee*.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.32 – 7.24 (m, 2H), 7.22 – 7.14 (m, 3H), 4.14 (q, *J* = 7.1 Hz, 2H), 2.62 (t, *J* = 8.0 Hz, 2H), 2.52 – 2.41 (m, 1H), 2.09 – 1.94 (m, 1H), 1.78 – 1.67 (m, 1H), 1.27 (t, *J* = 7.1 Hz, 3H), 1.19 (d, *J* = 7.0 Hz, 3H).

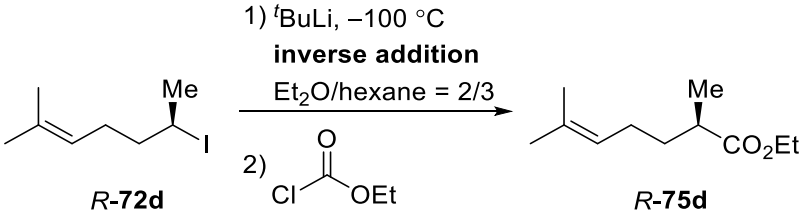
^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 176.7, 141.9, 128.6, 128.5, 126.0, 60.4, 39.2, 35.6, 33.6, 17.3, 14.4.

MS (70 eV, EI) *m/z* (%): 206 (22) $[M]^{+\bullet}$, 161 (31), 133 (6), 102 (100), 89 (76), 74 (45).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3027 (w), 2976 (w), 2935 (w), 1729 (s), 1604 (w), 1496 (w), 1454 (vs), 1377 (w), 1348 (w), 1240 (w), 1158 (m), 1123 (w), 1051 (w), 1028 (w), 858 (w), 746 (m), 697 (vs).

HRMS (EI) *m/z*: calcd for **$C_{13}H_{18}O_2^{+\bullet}$** $[M]^{+\bullet}$: 206.1307, found: 206.1311.

Optical rotation: $[\alpha]_D^{23}$= 2.4 (c 0.11, $CHCl_3$)



R-**72d** *R*-**75d**

R-**75d**

According to **Standard procedure C**, iodide *R*-**72d** (71.4 mg, 0.30 mmol) as a starting material and ethyl chloroformate (86 μL, 0.90 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/27 to afford *R*-**75d** (32.0 mg, 58% yield) as a colorless oil. The *ee* was determined on Daicel Chiralcel OB-H column with 2-propanol/heptane = 1/500, flow rate = 0.30 mL/min, temperature = 30 °C, wave length = 210 nm. Retention times: 17.7 min [minor enantiomer], 20.2 min [major enantiomer]. 97.3% *ee*.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.12 – 5.04 (m, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.49 – 2.36 (m, 1H), 2.03 – 1.93 (m, 2H), 1.76 – 1.66 (m, 1H), 1.68 (d, *J* = 1.4 Hz, 3H), 1.59 (s, 3H), 1.42 (dtd, *J* = 13.8, 7.7, 6.3 Hz, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H).

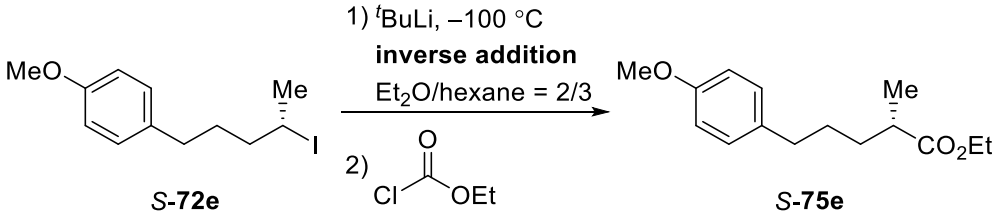
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 177.0, 132.3, 123.8, 60.3, 39.2, 34.0, 25.9, 25.8, 17.8, 17.3, 14.4.

MS (70 eV, EI) *m/z* (%): 184 (44) $[M]^{+\bullet}$, 139 (26), 102 (100), 74 (58), 55 (12).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2970 (w), 2926 (w), 2857 (w), 1732 (vs), 1454 (w), 1376 (w), 1350 (w), 1261 (w), 1154 (s), 1119 (w), 1060 (w), 1028 (w), 858 (w), 751 (w).

HRMS (EI) *m/z*: calcd for **$C_{11}H_{20}O_2^{+\bullet}$** $[M]^{+\bullet}$: 184.1463, found: 184.1465.

Optical rotation: $[\alpha]_D^{20}$= -28.2 (c 0.85, CH_2Cl_2), lit.[128] for *S*-enantiomer $[\alpha]_D^{20}$= 29.2 (c 2.3, CH_2Cl_2).



S-**72e** *S*-**75e**

S-**75e**

According to **Standard procedure C**, iodide *S*-**72e** (91.3 mg, 0.30 mmol) as a starting material and ethyl chloroformate (86 μL, 0.90 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/20 to afford *S*-**75e** (46.0 mg, 61% yield) as a colorless oil. The *ee* was determined on Daicel Chiralcel OB-H columns with 2-propanol/heptane = 1/100, flow rate = 0.50 mL/min, temperature = 30 °C, wave length = 224 nm. Retention times: 39.7 min [major enantiomer], 45.8 min [minor enantiomer]. 92.0% *ee*.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.10 – 7.06 (m, 2H), 6.84 – 6.80 (m, 2H), 4.12 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 2.55 (t, *J* = 7.6 Hz, 2H), 2.48 – 2.38 (m, 1H), 1.74 – 1.64 (m, 1H), 1.63 – 1.54 (m, 2H), 1.49 – 1.38 (m, 1H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.14 (d, *J* = 7.0 Hz, 3H).

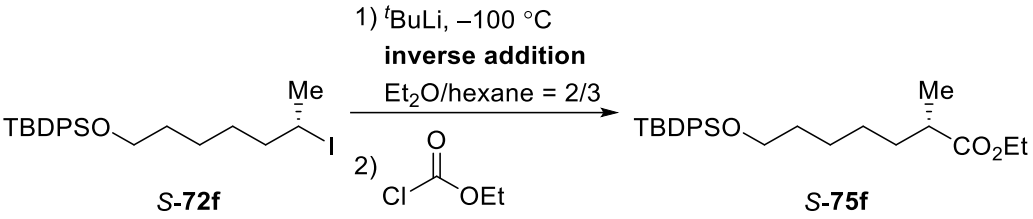
^{13}C-NMR (101 MHz, $CDCl_3$) δ: 176.9, 157.9, 134.5, 129.4, 113.9, 60.3, 55.4, 39.6, 35.0, 33.5, 29.4, 17.3, 14.4.

MS (70 eV, EI) *m/z* (%): 259 (25) $[M]^{+\bullet}$, 221 (35), 147 (29), 134 (33), 121 (100), 73 (20).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2977 (w), 2936 (w), 2859 (w), 2836 (w), 1729 (s), 1612 (w), 1584 (w), 1512 (vs), 1463 (m), 1444 (m), 1391 (w), 1377 (w), 1349 (w), 1300 (m), 1244 (vs), 1176 (s), 1153 (s), 1115 (m), 1096 (m), 1063 (m), 1035 (s), 931 (w), 830 (m), 809 (m), 748 (w), 714 (w), 699 (m).

HRMS (EI) *m/z*: calcd for **$C_{15}H_{22}O_3^{+\bullet}$** $[M]^{+\bullet}$: 250.1563, found: 250.1570.

Optical rotation: $[\alpha]_D^{23}$= 12.0 (c 1.10, $CDCl_3$)



S-**72f** *S*-**75f**

S-**75f**

According to **Standard procedure C**, iodide *S*-**72f** (144.1 mg, 0.30 mmol) as a starting material and ethyl chloroformate (86 μL, 0.90 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/20 to afford *S*-**75f** (79.2 mg, 62% yield) as a colorless oil. The *ee* was determined on Daicel Chiralcel OD-H columns with 2-propanol/heptane = 1/1000, flow rate = 0.30 mL/min, temperature = 30 °C, wave length = 224 nm. Retention times: 36.0 min [major enantiomer], 38.3 min [minor enantiomer]. 93.8% *ee*.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.71 – 7.65 (m, 4H), 7.46 – 7.37 (m, 6H), 4.13 (q, J = 7.1 Hz, 2H), 3.66 (t, J = 6.5 Hz, 2H), 2.41 (h, J = 7.0 Hz, 1H), 1.72 – 1.61 (m, 1H), 1.61 – 1.52 (m, 2H), 1.46 – 1.33 (m, 3H), 1.33 – 1.21 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H), 1.14 (d, J = 7.0 Hz, 3H), 1.06 (s, 9H).

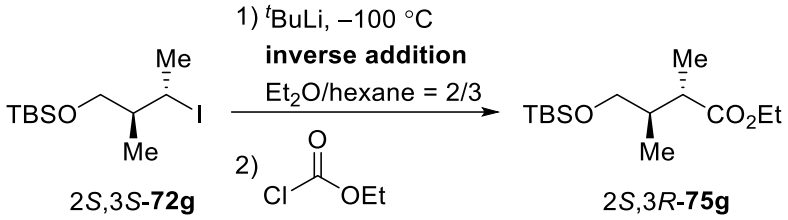
^{13}C-NMR (100 MHz, $CDCl_3$) δ: 177.1, 135.7, 134.2, 129.6, 127.7, 64.0, 60.2, 39.6, 33.9, 32.5, 27.1, 27.0, 25.9, 19.3, 17.2, 14.4.

MS (70 eV, EI) *m/z* (%): 369 (100) [M–^{t}Bu]$^{+\bullet}$, 323 (7), 263 (13), 227 (22), 199 (28), 183 (13), 167 (7), 139 (14), 105 (5), 55 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2932 (w), 2857 (w), 1732 (m), 1472 (w), 1462 (w), 1427 (w), 1389 (w), 1377 (w), 1255 (w), 1185 (w), 1173 (m), 1161 (w), 1105 (m), 1090 (m), 1029 (w), 1007 (w), 998 (w), 938 (w), 907 (w), 859 (w), 822 (w), 738 (w), 700 (vs), 686 (m).

HRMS (EI) *m/z*: calcd for **$C_{25}H_{35}O_3Si^{+\bullet}$** [M–Me]$^{+\bullet}$: 411.2355, found: 411.2340.

Optical rotation: $[\alpha]_D^{23}$= 4.9 (c 0.12, $CHCl_3$)



2*S*,3*S*-**72g** 2*S*,3*R*-**75g**

2S,3R-**75g**

According to **Standard procedure C**, iodide *2S,3S*-**72g** (108.3 mg, 0.33 mmol, dr=98:2, >99% *ee*) as a starting material and ethyl chloroformate (86 μL, 0.90 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/20 to afford *2S,3R*-**75g** (59.2 mg, 72% yield, dr=95:5, >99% *ee*) as a colorless oil.

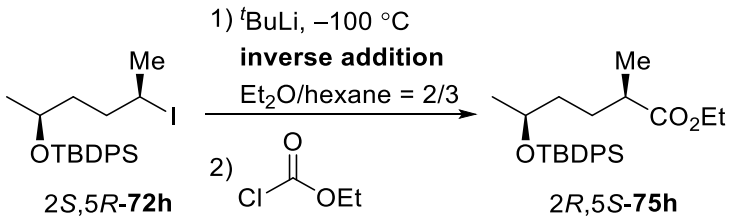
^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 4.16 – 4.07 (m, 2H), 3.61 – 3.47 (m, 2H), 2.49 (p, *J* = 7.0 Hz, 1H), 1.86 (dqd, *J* = 12.4, 6.8, 5.5 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.13 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.88 (s, 9H), 0.03 (s, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 176.3, 65.4, 60.1, 41.5, 38.9, 26.0, 18.4, 14.9, 14.7, 14.5, -5.3.

MS (70 eV, EI) *m/z* (%):2957 (w), 2930 (m), 2858 (w), 1733 (s), 1472 (w), 1463 (w), 1389 (w), 1374 (w), 1362 (w), 1251 (m), 1179 (m), 1158 (m), 1135 (m), 1094 (s), 1075 (s), 1032 (m), 1006 (m), 974 (w), 939 (w), 835 (vs), 814 (m), 774 (s), 666 (m).

HRMS (EI) *m/z*: calcd for **$C_{13}H_{27}O_3Si^{+\bullet}$** [M-$CH_3$]$^{+\bullet}$: 259.1729, found: 259.1719.

Optical rotation: $[\alpha]_D^{21}$= 36.2 (c 1.00, $CDCl_3$)



2R,5S-**75h**

According to **Standard procedure C**, iodide *2S,5R*-**72h** (140.1 mg, 0.30 mmol, dr=99:1, 99% *ee*) as a starting material and ethyl chloroformate (86 μL, 0.90 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/*i*hexane = 1/27→1/20 to afford *2R,5S*-**75h** (76.8 mg, 62% yield, dr=99:1, 99% *ee*) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.72 – 7.66 (m, 4H), 7.45 – 7.34 (m, 6H), 4.11 (q, *J* = 7.1 Hz, 2H), 3.84 (h, *J* = 5.9 Hz, 1H), 2.33 (h, *J* = 6.9, 6.4 Hz, 1H), 1.71 – 1.58 (m, 1H), 1.56 – 1.34 (m, 3H), 1.24 (t, *J* = 7.1 Hz, 3H), 1.14 – 1.00 (m, 15H).

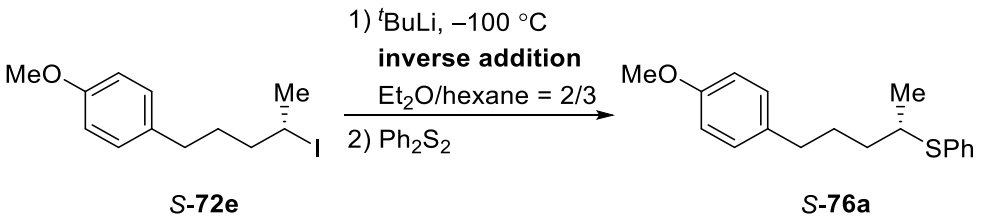
^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 176.9, 136.0, 134.9, 134.5, 129.6, 129.5, 127.6, 127.5, 69.6, 60.2, 39.7, 37.0, 29.5, 27.1, 23.3, 19.4, 17.1, 14.4.

MS (70 eV, EI) *m/z* (%): 412 (1) $[M]^{+\bullet}$, 371 (11), 355 (100), 309 (27), 277 (5), 249 (7), 227 (14), 199 (41), 183 (18), 167 (5), 139 (12), 105 (4), 83 (4), 55 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2966 (w), 2931 (w), 2857 (w), 1732 (m), 1472 (w), 1462 (w), 1427 (w), 1375 (w), 1258 (w), 1241 (w), 1213 (w), 1177 (m), 1131 (w), 1104 (m), 1057 (m), 1027 (w), 1005 (w), 996 (w), 937 (w), 881 (w), 865 (w), 821 (w), 739 (m), 700 (vs), 686 (m).

HRMS (EI) *m/z*: calcd for **$C_{25}H_{36}O_3Si^{+\bullet}$** $[M]^{+\bullet}$: 412.2434, found: 412.2426.

Optical rotation: $[\alpha]_D^{23}$= –45.9 (c 0.15, $CHCl_3$)



S-**72e** *S*-**76a**

S-**76a**

According to **Standard procedure C**, iodide *S*-**72e** (91.1 mg, 0.30 mmol) as a starting material and diphenyl disulfide (164.2 mg, 0.75 mmol) solved in Et_2O (0.60 ml) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/*i*hexane = 1/60 to afford *S*-**76a** (55.8 mg, 65% yield) as a colorless oil. The *ee* was determined on Daicel Chiralcel OB-H columns with 2-propanol/heptane = 1/50, flow rate = 0.60 mL/min, temperature = 30 °C, wave length = 224 nm. Retention times: 20.1 min [major enantiomer], 31.8 min [minor enantiomer]. 94.0% *ee*.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.32 – 7.24 (m, 2H), 7.22 – 7.10 (m, 3H), 7.03 – 6.96 (m, 2H), 6.77 – 6.70 (m, 2H), 3.70 (s, 3H), 3.12 (h, *J* = 6.7 Hz, 1H), 2.46 (t, *J* = 7.6 Hz, 2H), 1.74 – 1.62 (m, 2H), 1.61 – 1.51 (m, 1H), 1.51 – 1.39 (m, 1H), 1.18 (d, *J* = 6.7 Hz, 3H).

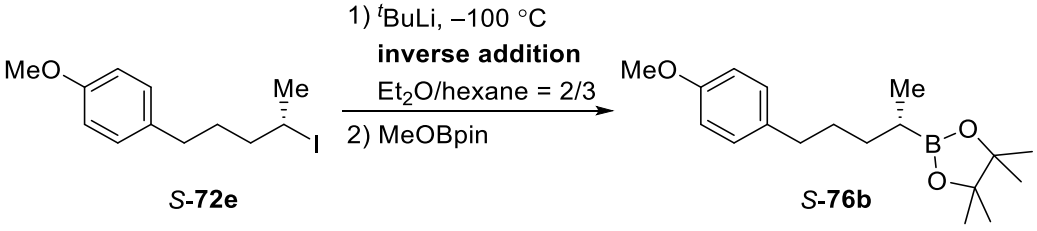
^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 157.8, 135.4, 134.4, 132.2, 129.4, 128.9, 126.8, 113.8, 55.4, 43.4, 36.2, 34.9, 29.2, 21.3.

MS (70 eV, EI) *m/z* (%): 286 (36) $[M]^{+\bullet}$, 177 (15), 138 (36), 121 (100), 77 (8).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3001 (w), 2930 (w), 2856 (w), 2834 (w), 1611 (w), 1583 (w), 1510 (s), 1479 (w), 1462 (w), 1438 (w), 1374 (w), 1299 (w), 1242 (vs), 1176 (m), 1114 (w), 1091 (w), 1067 (w), 1035 (m), 1025 (m), 1000 (w), 828 (w), 807 (m), 778 (w), 738 (s), 691 (s).

HRMS (EI) *m/z*: calcd for **$C_{18}H_{22}OS^{+\bullet}$** $[M]^{+\bullet}$: 286.1391, found: 286.1392.

Optical rotation: $[\alpha]_D^{23}$= –16.7 (c 0.12, $CHCl_3$)



S-**72e** *S*-**76b**

R-**76b**

According to **Standard procedure C**, iodide *S*-**72e** (91.2 mg, 0.30 mmol) as a starting material and methoxyboronic acid pinacol ester (0.15 mL, 0.90 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/*i*hexane = 1/15 to afford *R*-**76b** (60.3 mg, 66% yield) as a colorless oil. The *ee* was determined by using transformations described below.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.12 – 7.06 (m, 2H), 6.85 – 6.79 (m, 2H), 3.78 (s, 3H), 2.54 (t, *J* = 7.4 Hz, 2H), 1.66 – 1.55 (m, 2H), 1.55 – 1.45 (m, 1H), 1.41 – 1.28 (m, 1H), 1.23 (s, 12H), 1.10 – 0.99 (m, 1H), 0.96 (d, *J* = 6.9 Hz, 3H).

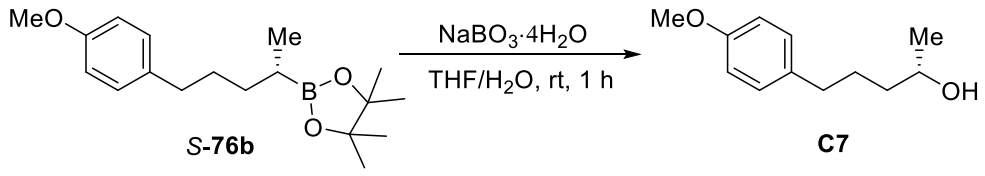
^{13}C-NMR (100 MHz, $CDCl_3$) *δ*: 157.7, 135.2, 129.3, 113.7, 83.0, 55.4, 35.4, 33.0, 31.3, 24.9, 24.9, 15.6.

MS (70 eV, EI) *m/z* (%): 304 (66) $[M]^{+\bullet}$, 220 (5), 204 (85), 177 (5), 138 (14), 121 (100), 91 (5), 77 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2977 (w), 2929 (w), 2854 (w), 1612 (w), 1512 (s), 1463 (w), 1405 (w), 1380 (m), 1370 (m), 1313 (m), 1243 (s), 1215 (w), 1175 (w), 1166 (w), 1142 (vs), 1113 (w), 1037 (m), 966 (w), 863 (w), 853 (m), 841 (w), 827 (w), 806 (w), 748 (w), 686 (w), 670 (w).

HRMS (EI) *m/z*: calcd for **$C_{18}H_{29}O_3B^{+\bullet}$** $[M]^{+\bullet}$: 304.2210, found: 304.2208.

Optical rotation: $[\alpha]_D^{23}$= 1.5 (c 0.42, $CHCl_3$)



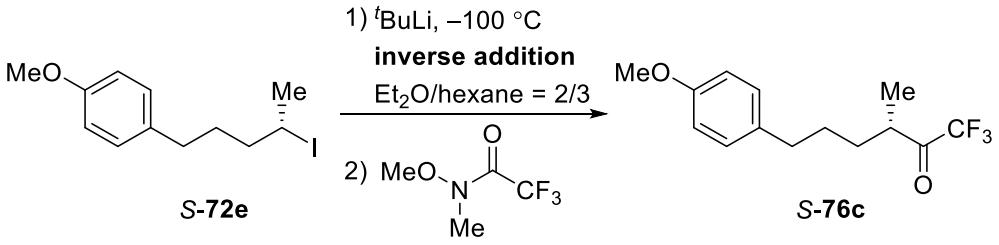
S-**76b** **C7**

C7

A flame-dried 25 mL flask was charged with boronic ester *R*-**76b** (24.2 mg, 0.08 mmol) in THF (1 mL) and H_2O (1 mL). $NaBO_3{\cdot}4H_2O$ (18.4 mg, 0.12 mmol) was added and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was quenched with H_2O

and extracted with Et_2O (3×10 mL). The combined organic phases were dried over $MgSO_4$ and solvents were evaporated. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/1 to afford **C7** (13.2 mg, 85% yield) as a colorless oil. The *ee* was determined on Daicel Chiralcel OB-H column with 2-propanol/heptane = 1/20, flow rate = 0.50 mL/min, temperature = 30 °C, wave length = 254 nm. Retention times: 29.7 min [minor enantiomer], 35.8 min [major enantiomer]. 93.2% *ee*. The analytical data except optical rotation were identical to those of *R*-**73e**.

Optical rotation: $[\alpha]_D^{23}$= 18.0 (c 0.15, $CHCl_3$)



S-**76c**

According to **Standard procedure C**, iodide *S*-**72e** (94.2 mg, 0.31 mmol) as a starting material and $CF_3CON(OMe)Me$ (109 μL, 0.90 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/20 to afford *S*-**76c** (51.0 mg, 60% yield) as a colorless oil. The *ee* was determined on Daicel Chiralcel OD-H columns with 2-propanol/heptane = 1/1000, flow rate = 0.60 mL/min, temperature = 30 °C, wave length = 224 nm. Retention times: 20.1 min [major enantiomer], 21.8 min [minor enantiomer]. 91.0% *ee*.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.12 – 7.04 (m, 2H), 6.86 – 6.79 (m, 2H), 3.79 (s, 3H), 3.04 – 2.94 (m, 1H), 2.62 – 2.49 (m, 2H), 1.87 – 1.74 (m, 1H), 1.66 – 1.41 (m, 3H), 1.20 (d, *J* = 7.0 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 195.42 (q, *J* = 33.5 Hz), 158.0, 133.8, 129.3, 115.51 (q, *J* = 293.1, 292.7 Hz), 114.0, 111.5, 55.4, 40.9, 34.9, 32.0, 29.0, 16.2.

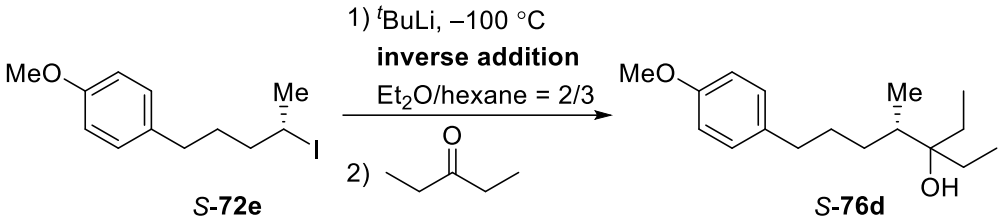
^{19}F NMR (376 MHz, $CDCl_3$) *δ*: -78.0.

MS (70 eV, EI) *m/z* (%): 274 (12) $[M]^{+\bullet}$, 147 (6), 134 (4), 121 (100), 91 (4), 77 (4).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2939 (w), 2861 (vw), 2838 (vw), 1756 (m), 1613 (w), 1584 (w), 1512 (s), 1464 (m), 1443 (w), 1382 (vw), 1300 (m), 1282 (w), 1245 (s), 1204 (s), 1177 (s), 1146 (vs), 1036 (s), 1009 (m), 983 (s), 909 (w), 830 (m), 810 (m), 791 (w), 748 (w), 736 (w), 714 (w), 700 (m), 671 (w).

HRMS (EI) *m/z*: calcd for **$C_{14}H_{17}O_2F_3^{+\bullet}$** $[M]^{+\bullet}$: 274.1181, found: 274.1189.

Optical rotation: $[\alpha]_D^{23}$= 110.7 (c 0.46, $CDCl_3$)



S-**76d**

According to **Standard procedure C**, iodide *S*-**72e** (91.3 mg, 0.30 mmol) as a starting material and diethyl ketone (78 μL, 0.90 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with EtOAc/*i*hexane = 1/10 to afford *S*-**76d** (40.1 mg, 51% yield) as a colorless oil. The *ee* was determined on Daicel Chiralcel OD-H columns with 2-propanol/heptane = 1/50, flow rate = 0.50 mL/min, temperature = 30 °C, wave length = 224 nm. Retention times: 12.9 min [major enantiomer], 13.7 min [minor enantiomer]. 93.2% *ee*.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.13 – 7.07 (m, 2H), 6.86 – 6.79 (m, 2H), 3.79 (s, 3H), 2.65 – 2.45 (m, 2H), 1.81 – 1.67 (m, 1H), 1.63 – 1.39 (m, 8H), 1.03 (s, 1H), 0.89 – 0.82 (m, 9H).

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 157.8, 135.0, 129.3, 113.8, 76.4, 55.4, 39.3, 35.6, 30.8, 30.6, 28.2, 28.1, 13.8, 7.7, 7.6.

MS (70 eV, EI) *m/z* (%): 246 (12) $[M\text{-}OH]^{+\bullet}$, 235 (9), 217 (12),178 (19), 147 (11), 134 (71), 121 (100), 91 (8), 87 (10), 77 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3488 (vw), 2965 (m), 2936 (m), 2881 (w), 2859 (w), 2835 (w), 1612 (w), 1584 (w), 1511 (vs), 1461 (m), 1442 (m), 1420 (w), 1379 (w), 1300 (m), 1243 (vs), 1176 (m), 1116 (m), 1036 (s), 943 (s), 925 (m), 829 (m), 807 (m), 774 (w), 750 (m), 696 (w)

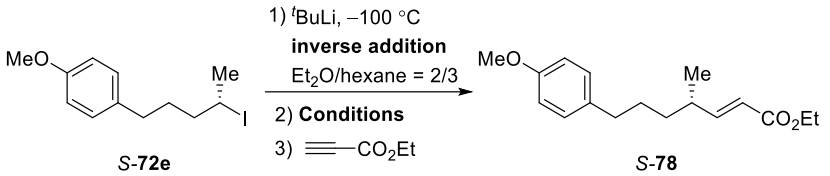
HRMS (EI) *m/z*: calcd for $\mathbf{C_{17}H_{28}O_2^{+\bullet}}$ $[M]^{+\bullet}$: 264.2089, found: 264.2095.

Optical rotation: $[\alpha]_D^{23}$= -22.7 (c 0.90, $CDCl_3$)

[General procedure D]

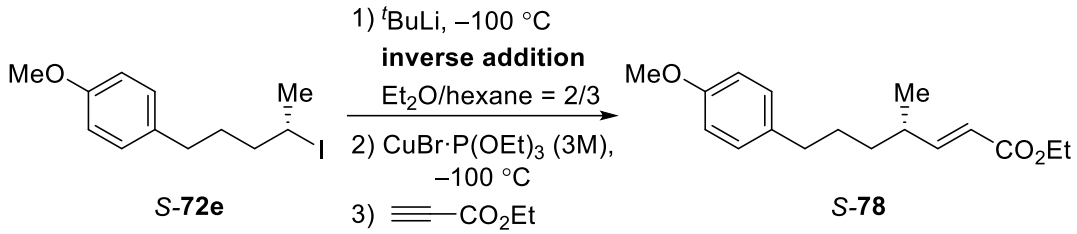
A flame-dried and Ar-flushed *Schlenk*-tube was cooled down to −100 °C and charged with a solution of ^{t}BuLi (0.34 mL, 2.22 M in pentane, 0.75 mmol) in mixture of Et_2O (1.50 mL) and ^{n}hexane (2.30 mL). A solution of alkyl iodide (0.30 mmol) in Et_2O (0.60 mL) was added dropwise in 1 min. After stirring for 10 sec, a solution of $CuBr{\cdot}P(OEt)_3$ (0.20 mL, 3.0 M in Et_2O, 0.60 mmol) was added and the reaction mixture was stirred for 1 min at −100 °C to observe the color change from yellow to green or orange. Then electrophile (0.60 mmol) was added at −100 °C and the reaction mixture was warmed to −80 °C in1 h. After quenching the reaction mixture with aq. NH_3 solution (or other solution, see below), the reaction mixture was extracted with Et_2O (3×10 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The obtained crude product was purified by column chromatography.

Table 4. Optimization of the reaction conditions.



S-**72e** *S*-**78**

Entry	$CuBr{\cdot}P(OEt)_3$ Molarity and equiv.	Temperature	Time	Isolated yield and *ee*
1	1 M in Et_2O, 2.0 equiv.[125]	– 100 °C to – 80 °C	1 h	42%, 82.1% *ee*
2	3 M in Et_2O, 2.0 equiv.	– 100 °C to – 80 °C	1 h	47%, 92.2% *ee*
3	neat, 2.0 equiv.	– 100 °C to – 80 °C	1 h	35%, 80.0% *ee*



S-**78**

According to **Standard procedure D**, iodide *S*-**72e** (91.0 mg, 0.30 mmol, 98% *ee*) as a starting material and ethyl propiolate (91 μL, 0.90 mmol) as an electrophile were used. The reaction mixture was quenched with few drops of acetic acid. The crude product was purified by column chromatography on silica gel with Et_2O/*i*hexane = 1/15 to afford *S*-**78** (39.1 mg, 47% yield) as a colorless oil. The *ee* was determined on Daicel Chiralcel OB-H columns with 2-propanol/heptane = 1/100, flow rate = 0.50 mL/min, temperature = 30 °C, wave length = 224 nm. Retention times: 31.3 min [minor enantiomer], 35.8 min [major enantiomer]. 92.2% *ee*.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.13 – 7.02 (m, 2H), 6.88 – 6.80 (m, 3H), 5.76 (dd, *J* = 15.7, 1.2 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 2.53 (t, *J* = 7.5 Hz, 2H), 2.30 (ddtd, *J* = 13.5, 8.0, 6.8, 1.2 Hz, 1H), 1.63 – 1.52 (m, 2H), 1.46 – 1.35 (m, 2H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.04 (d, *J* = 6.8 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 167.0, 157.9, 154.5, 134.5, 129.4, 119.9, 113.9, 60.3, 55.4, 36.6, 35.7, 35.1, 29.4, 19.5, 14.4.

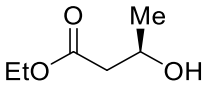
MS (70 eV, EI) *m/z* (%): 276 (9) $[M]^{+\bullet}$, 202 (6), 147 (36), 134 (31), 121 (100), 108 (3), 91 (5), 77 (5).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2932 (w), 2857 (w), 1715 (vs), 1651 (m), 1612 (w), 1584 (w), 1512 (s), 1463 (m), 1444 (w), 1391 (w), 1367 (m), 1346 (w), 1300 (m), 1265 (s), 1243 (vs), 1176 (s), 1147 (m), 1114 (m), 1096 (m), 1035 (s), 984 (m), 866 (m), 829 (m), 808 (m), 750 (w), 724 (m), 699 (m).

HRMS (EI) *m/z*: calcd for **$C_{17}H_{24}O_3^{+\bullet}$** $[M]^{+\bullet}$: 276.1725, found: 276.1732.

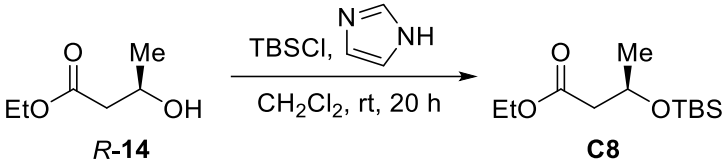
Optical rotation: $[\alpha]_D^{23}$= 70.9 (c 0.77, $CDCl_3$)

Total synthesis of (-)-lardolure (70) and siphonarienal (71)



R-**80**

The *ee* of ethyl (*R*)-3-hydroxybutyrate *R*-**80** was determined using GC with *CP-ChiraSil -DEX CB* column with 0.40 mL/min flow rate; temperature = 40 °C; average velocity = 20; 5 °C/min heating rate and holding time 5 min. Retention times: 29.41 min [minor enantiomer], 30.05 min [major enantiomer]. >99% *ee*.

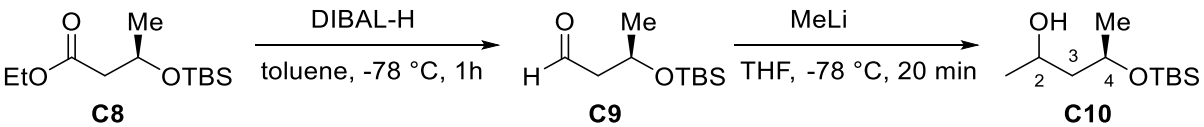


R-**14** **C8**

C8

To a solution of ethyl (*R*)-3-hydroxybutyrate *R*-**80** (2.60 mL, 20.0 mmol, >99% *ee*) in CH_2Cl_2 (50 mL) was added imidazole (2.70 g, 40.0 mmol) in one portion and TBSCl (3.61 g, 24.0 mmol) in one portion at room temperature. The reaction mixture was stirred at room temperature for 20 h. Then the reaction mixture was quenched with water (30 mL). The layers were separated and the aqueous phase was extracted with Et_2O (3×100 mL). The organic phases were combined and dried over $MgSO_4$. The solvents were evaporated and the crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/20 to afford **C8** (4.88 g, 99% yield, >99% *ee*) as a colorless oil. The analytical data was identical to the literature values.[129]

^{1}H NMR (400 MHz, $CDCl_3$) *δ*: 4.32 – 4.23 (m, 1H), 4.11 (qd, *J* = 7.1, 4.0 Hz, 2H), 2.46 (dd, *J* = 14.5, 7.6 Hz, 1H), 2.35 (dd, *J* = 14.5, 5.3 Hz, 1H), 1.25 (t, *J* = 7.2 Hz, 3H), 1.19 (d, *J* = 6.1 Hz, 3H), 0.86 (s, 8H), 0.06 (s, 3H), 0.04 (s, 3H).



C8 **C9** **C10**

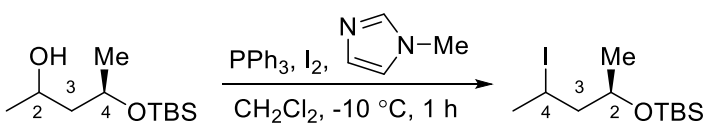
C10

To a solution of **C8** (4.75 g, 19.3 mmol, >99% *ee*) in toluene (100 mL) was added a solution DIBAL-H (20.3 mL, 1.0 M in heptane, 20.3 mmol) dropwise in 30 min using syringe pump at -78°C (flow = 40 mL/h). The reaction mixture was stirred for another 30 min at -78 °C and then it was quenched with MeOH (10 mL). After warming the reaction mixture to room temperature and a sat. aq. Rochelle salt solution was added. The formed suspension was mixed for 2 h until complete phase separation and then the aqueous phase was extracted with Et_2O (3×150 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product **C9** (3.82 g, 98% yield) was used for the next step without any additional purification.

To a solution of the aldehyde **C9** (3.82 g, 18.9 mmol) in THF (40 mL) was added a solution of MeLi (10.9 mL, 2.07 M in Et_2O, 22.7 mmol) dropwise in 15 min using syringe pump at -78 °C (flow = 40.0 mL/h). The reaction mixture was stirred for another 20 min at –78 °C and then it was gradually warmed to room temperature. The reaction mixture was quenched with sat. aq. NH_4Cl solution. The layers were separated and the aqueous phase was extracted with Et_2O (3×100 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/4 to afford **C10** (3.67 g, 89% yield, >99% *ee*) as a colorless oil. The reported analytical data correspond to two diastereomers at C(2) in ratio 1:1. Other analytical data was identical to the literature values.[74]

^{1}H NMR (600 MHz, $CDCl_3$) *δ*: 4.23 – 4.13 (m, 2H), 4.11 – 4.04 (m, 1H), 3.99 – 3.91 (m, 1H), 3.48 (s, 1H), 3.40 (s, 1H), 1.70 – 1.45 (m, 4H), 1.23 (d, *J* = 6.3 Hz, 3H), 1.19 – 1.14 (m, 9H), 0.90 (s, 9H), 0.89 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.09 (s, 3H), 0.08 (s, 3H).

Optical rotation: $[\alpha]_D^{21}$= -39.8 (c 0.90, $CDCl_3$)



C10 *2R,4RS*-**81**

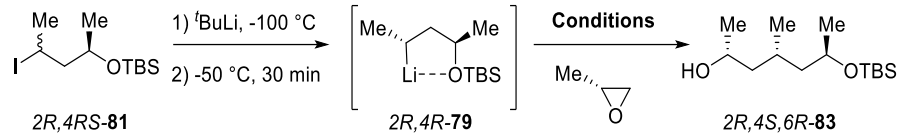
2R,*4RS*-**81**

According to **Standard procedure B**, alcohol **C10** (2.00 g, 9.2 mmol, >99% *ee*) as a starting material was used. The crude product was purified by column chromatography on silica gel with $Et_2Oc/^{i}$hexane = 1/100 to afford 2*R*,4*RS*-**81** (2.52 g, 84% yield, >99% *ee*) as a colorless oil. The reported analytical data correspond to two diastereomers at C(4) in ratio 1:1. Other analytical data was identical to the literature values.[74]

^{1}H-NMR (600 MHz, $CDCl_3$) *δ*: 4.32 – 4.23 (m, 1H), 4.16 (dp, *J* = 8.0, 6.8 Hz, 1H), 3.99 – 3.88 (m, 2H), 2.23 – 2.13 (m, 1H), 1.96 (d, *J* = 6.9 Hz, 3H), 1.93 (d, *J* = 6.8 Hz, 3H), 1.86 (ddd, *J* = 14.7, 11.1, 2.3 Hz, 1H), 1.74 – 1.65 (m, 1H), 1.56 – 1.48 (m, 1H), 1.17 (d, *J* = 6.1 Hz, 3H), 1.12 (d, *J* = 6.0 Hz, 3H), 0.89 (s, 18H), 0.14 (s, 3H), 0.10 (s, 3H), 0.07 (s, 3H), 0.07 (s, 3H).

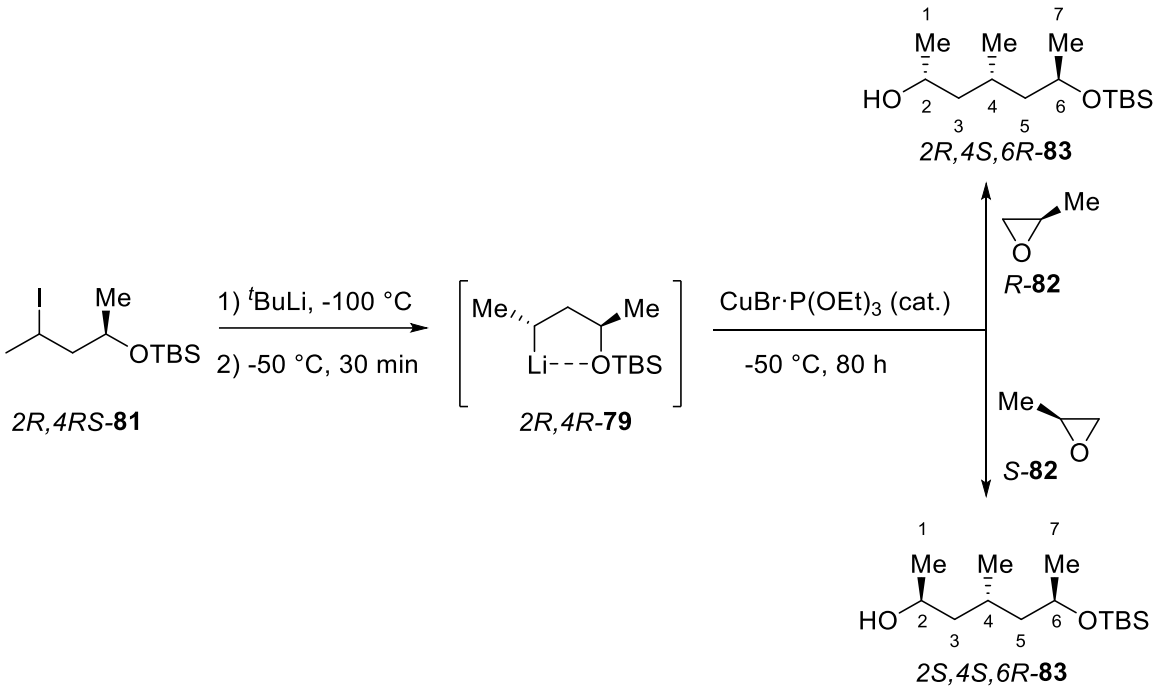
Optical rotation: $[\alpha]_D^{21}$= -46.9 (c 0.90, $CDCl_3$)

Table 5. Optimization of the reaction conditions.



2R,4RS-**81** *2R,4R*-**79** *2R,4S,6R*-**83**

Entry	$CuBr \cdot P(OEt)_3$ Molarity and equiv.	Temperature	Time	Additives	Scale	Yield and dr
1	-	– 50 °C	1 h	-	0.30 mmol	0%
2	-	– 50 °C	1 h	$BF_3 \cdot OEt_2$	0.30 mmol	0%
3	1 M in Et_2O, 2.0 equiv.	– 100 °C to – 30 °C	1 h	-	0.30 mmol	42%, 93:7
4	3 M in Et_2O, 2.0 equiv.	– 50 °C to – 30 °C	1 h	-	0.30 mmol	58%, 93:7
5	3 M in Et_2O, 2.0 equiv.	– 50 °C to – 30 °C	1 h	-	0.60 mmol	55%, 80:20
6	neat, 2.0 equiv.	– 50 °C to – 30 °C	1 h	-	0.30 mmol	33%, 90:10
6	3 M in Et_2O, 0.3 equiv.	– 30 °C	48 h	-	1.00 mmol	54%, 92:8
6	3 M in Et_2O, 0.3 equiv.	- 50 °C	48 h	-	1.00 mmol	60%, 98:2



2*R*,4*S*,6*R*-**83** and 2*S*,4*S*,6*R*-**83**

A flame-dried and Ar-flushed *Schlenk*-tube was cooled down to –100 °C and charged with a solution of ^{t}BuLi (11.2 mL, 2.22 M in pentane, 25.0 mmol) in mixture of Et_2O (14.0 mL) and *n*-hexane (56.0 mL). A solution of alkyl iodide 2*R*,4*RS*-**81** (3.28 g, 10.0 mmol, dr=1:1, >99% *ee*) in a mixture of Et_2O (9.0 mL) and ^{n}hexane (14.0 mL) was added dropwise using syringe pump (rate = 40 mL/h). Then the reaction mixture was warmed to –50 °C and stirred at this temperature for 30 min. Then a solution of $CuBr{\cdot}P(OEt)_3$ (1.00 mL, 3.0 M in Et_2O, 3.0 mmol) and (*R*)-propylene oxide (*R*-**82**) or (*S*)-propylene oxide (*S*-**82**) (0.21 mL, 30.0 mmol) were added and the reaction mixture was stirred for 50 h at –50 °C. After quenching the reaction mixture with aq. NH_3 solution, the reaction mixture was extracted with Et_2O (3×30 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The obtained crude product was purified by column chromatography.

2*R*,4*S*,6*R*-**83**

The diastereomeric ratio of the crude product 2*R*,4*S*,6*R*-**83** at C(4) is 98:2 and diastereomers can be separated using the column chromatography. The crude product 2*R*,4*S*,6*R*-**83** was purified by column chromatography on silica gel with EtOAc/^{i}hexane = 1/8 to afford 2*R*,4*S*,6*R*-**83** (1.56 g, 60% yield, dr=99:1, >99% *ee*) as a colorless oil. The *ee* was determined using Mosher's ester analysis.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.99 – 3.80 (m, 2H), 1.78 – 1.62 (m, 1H), 1.50 (ddd, *J* = 13.9, 9.1, 4.8 Hz, 1H), 1.43 – 1.24 (m, 3H), 1.18 (d, *J* = 6.1 Hz, 3H), 1.18 – 1.15 (m, 1H), 1.12 (d, *J* = 6.0 Hz, 3H), 0.91 (d, *J* = 6.6 Hz, 3H), 0.88 (s, 9H), 0.06 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$) δ: 66.9, 65.8, 47.9, 47.2, 26.6, 26.1, 24.5, 23.8, 19.9, 18.3, -4.2, -4.4.

MS (70 eV, EI) *m/z* (%): 201 (5) $[M\text{-}t\text{Bu}]^{+\bullet}$, 185 (3), 159 (16), 119 (56), 111 (23), 75 (68), 69 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3324 (m), 2962 (m), 2927 (m), 2857 (w), 1462 (m), 1408 (w), 1374 (m), 1343 (m), 1318 (w), 1252 (m), 1130 (s), 1063 (m), 1022 (w), 1001 (m), 974 (w), 945 (m), 920 (m), 874 (s), 834 (vs), 773 (s), 724 (m), 712 (m), 667 (m).

HRMS (EI) *m/z*: calcd for **$C_{13}H_{27}OSi^{+\bullet}$** $[M\text{-}CH_3\text{-}H_2O]^{+\bullet}$: 227.1831, found: 227.1821.

Optical rotation: $[\alpha]_D^{20}$= -16.0 (c 0.40, $CDCl_3$)

2*S*,4*S*,6*R*-**83**

The diastereomeric ratio of the crude product 2*S*,4*S*,6*R*-**83** at C(4) is 97:3 and diastereomers can be separated using the column chromatography. The crude product 2*S*,4*S*,6*R*-**83** was purified by column chromatography on silica gel with EtOAc/^{i}hexane = 1/8 to afford 2*S*,4*S*,6*R*-**83** (1.51 g, 58% yield, dr=99:1, >99% *ee*) as a colorless oil. The compound decomposes to the corresponding diol slowly in $CDCl_3$. The *ee* was determined using Mosher's ester analysis.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 3.97 – 3.85 (m, 2H), 1.66 (dq, *J* = 13.5, 6.8 Hz, 1H), 1.50 (s, 1H), 1.47 – 1.26 (m, 5H), 1.18 (d, *J* = 6.2 Hz, 3H), 1.13 (d, *J* = 6.0 Hz, 3H), 0.91 (d, *J* = 6.8 Hz, 3H), 0.89 (s, 9H), 0.06 (s, 6H).

^{1}H NMR (400 MHz, C_6D_6) δ: 3.87 (h, *J* = 6.2 Hz, 1H), 3.72 – 3.62 (m, 1H), 1.80 – 1.64 (m, 1H), 1.46 – 1.31 (m, 2H), 1.25 – 1.19 (m, 2H), 1.12 (d, *J* = 6.0 Hz, 3H), 1.01 (d, *J* = 6.2 Hz, 3H), 1.01 (s, 9H), 0.88 (d, *J* = 6.8 Hz, 3H), 0.10 (s, 3H), 0.09 (s, 3H).

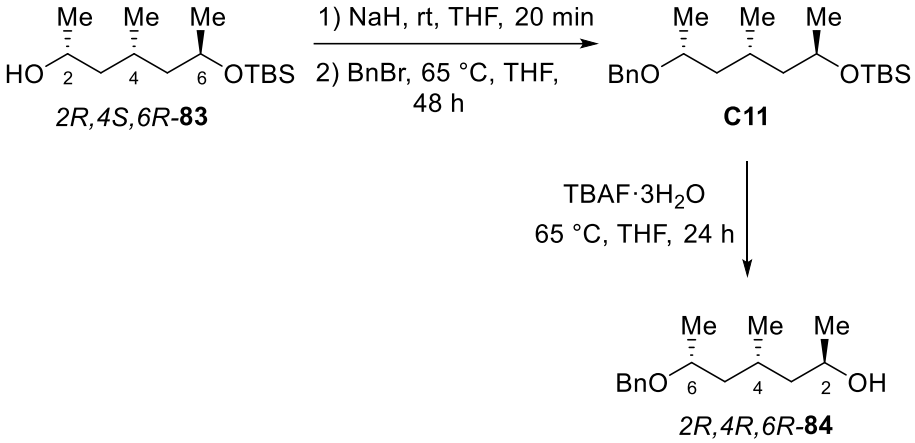
^{13}C-NMR (101 MHz, C_6D_6) δ: 67.3, 65.6, 47.6, 47.3, 27.0, 26.2, 24.2, 24.0, 21.2, 18.3, -4.0, -4.4.

MS (70 eV, EI) *m/z* (%): 201 (2) [M-*t*Bu]$^{+\bullet}$, 185 (16), 159 (10), 141 (6), 119 (31), 111 (6), 95 (12), 75 (100), 69 (36).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3332 (w), 2958 (m), 2928 (m), 2858 (m), 1472 (w), 1462 (m), 1432 (w), 1408 (w), 1374 (m), 1254 (m), 1148 (m), 1122 (m), 1072 (s), 1038 (m), 1006 (s), 984 (m), 960 (m), 940 (m), 900 (m), 874 (w), 834 (vs), 806 (m), 772 (vs), 718 (m), 662 (m).

HRMS (EI) *m/z*: calcd for **$C_{13}H_{27}OSi^{+\bullet}$** [M-$CH_3$-$H_2O$]$^{+\bullet}$: 227.1831, found: 227.1822.

Optical rotation: $[\alpha]_D^{20}$= 1.4 (c 0.83, $CHCl_3$)



2R,4R,6R-**84**

To a solution of alcohol 2*R*,4*S*,6*R*-**83** (1.19 g, 4.57 mmol, >99% *ee*) in THF (50 mL) a suspension of NaH (0.29 g, 60 wt% in mineral oil, 7.31 mmol) at room temperature. Then benzyl bromide (0.87 mL, 7.31 mmol) was added and reaction mixture was refluxed for 48 h. Then the reaction was cooled to room temperature and quenched with sat. aq. NH_4Cl solution. The reaction mixture was extracted with Et_2O (3×100 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The obtained crude product was used in the next step without any additional purification.

To a solution of compound **C11** in THF (100 mL) was added TBAF·3H_2O (5.78 g, 18.28 mmol) and the resulting reaction mixture was refluxed for 24 h. Then the reaction mixture was cooled to room temperature and quenched with water. The reaction mixture was extracted with Et_2O (3×100 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by column chromatography on silica gel with

EtOAc/^{i}hexane = 1/5 to afford *2R,4R,6R*-**84** (0.86 g, 77% yield over 2 steps, dr>99:1, >99% *ee*) as a colorless oil.

^{1}H-NMR (600 MHz, $CDCl_3$) δ: 7.35 – 7.32 (m, 4H), 7.30 – 7.26 (m, 1H), 4.61 (d, *J* = 11.6 Hz, 1H), 4.41 (d, *J* = 11.6 Hz, 1H), 3.94 – 3.85 (m, 1H), 3.60 (dqd, *J* = 9.5, 6.0, 3.5 Hz, 1H), 1.90 – 1.77 (m, 2H), 1.69 (ddd, *J* = 14.0, 9.5, 4.0 Hz, 1H), 1.38 (ddd, *J* = 13.5, 8.0, 6.5 Hz, 1H), 1.28 (ddd, *J* = 13.5, 7.8, 5.3 Hz, 1H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.15 (d, *J* = 6.2 Hz, 3H), 1.12 (ddd, *J* = 14.0, 8.7, 3.5 Hz, 1H), 0.87 (d, *J* = 6.6 Hz, 3H).

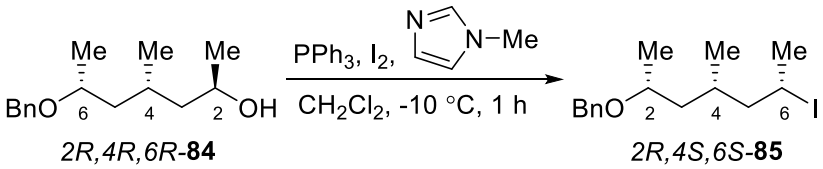
^{13}C-NMR (151 MHz, $CDCl_3$) δ: 138.9, 128.5, 128.0, 127.7, 73.0, 70.6, 65.6, 47.3, 44.2, 26.5, 23.6, 20.7, 20.2.

MS (70 eV, EI) *m/z* (%): 236 (5) $[M]^{+\bullet}$, 154 (12), 127 (8), 111 (80), 107 (11), 91 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3406 (w), 3030 (vw), 2964 (m), 2926 (m), 2871 (w), 1496 (w), 1454 (m), 1430 (w), 1373 (m), 1342 (w), 1309 (w), 1246 (w), 1206 (w), 1124 (m), 1085 (m), 1066 (s), 1028 (m), 999 (m), 972 (w), 941 (m), 915 (m), 880 (w), 846 (w), 830 (w), 789 (w), 734 (s), 696 (vs).

HRMS (EI) *m/z*: calcd for **$C_{15}H_{22}O^{+\bullet}$** $[M\text{-}H_2O]^{+\bullet}$: 218.1671, found: 218.1716.

Optical rotation: $[\alpha]_D^{22}$= -29.1 (c 0.57, $CDCl_3$)



2R,4R,6R-**84** *2R,4S,6S*-**85**

2*R*,4*S*,6*S*-**85**

According to **Standard procedure B**, alcohol *2R,4R,6R*-**84** (0.71 g, 3.00 mmol, dr > 99:1, >99% *ee*) as a starting material was used. The crude product was purified by column chromatography on silica gel with Et_2Oc/^{i}hexane = 1/100 to afford 2*R*,4*S*,6*S*-**85** (0.82 g, 79% yield, dr > 99:1, >99% *ee*) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.39 – 7.31 (m, 4H), 7.30 – 7.26 (m, 1H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.43 (d, *J* = 11.7 Hz, 1H), 4.21 (dqd, *J* = 10.0, 6.8, 4.4 Hz, 1H), 3.66 – 3.55 (m, 1H), 1.94

(d, *J* = 6.8 Hz, 3H), 1.97 – 1.84 (m, 2H), 1.62 (ddd, *J* = 13.7, 8.3, 5.3 Hz, 1H), 1.30 – 1.24 (m, 1H), 1.22 (d, *J* = 6.0 Hz, 3H), 1.20 – 1.16 (m, 1H), 0.81 (d, *J* = 6.3 Hz, 3H).

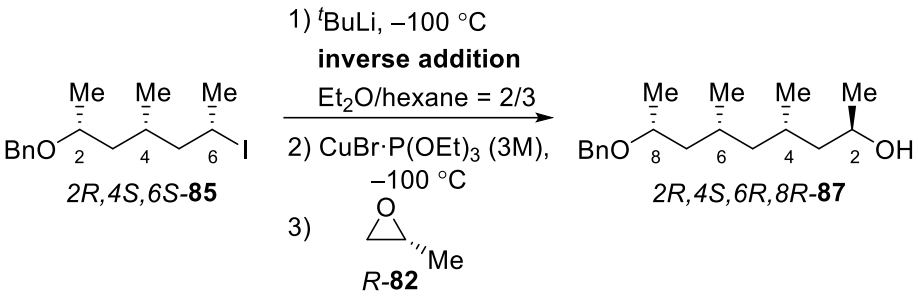
^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 139.1, 128.5, 127.9, 127.6, 72.8, 70.5, 50.4, 44.5, 30.6, 29.7, 29.4, 20.2, 18.9.

MS (70 eV, EI) *m/z* (%): 255 (1) $[M\text{-}Bn]^{+\bullet}$, 159 (2), 135 (6), 127 (11), 91 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2964 (m), 2923 (m), 2866 (w), 1496 (w), 1453 (m), 1375 (m), 1341 (w), 1306 (w), 1261 (w), 1218 (w), 1174 (m), 1161 (m), 1139 (s), 1108 (m), 1089 (m), 1065 (s), 1028 (m), 991 (w), 961 (w), 928 (w), 908 (w), 859 (w), 839 (w), 824 (w), 793 (w), 733 (vs), 696 (vs).

HRMS (ESI+) *m/z*: calcd for **$C_{15}H_{27}ONI^{+\bullet}$** $[M+NH_4]^{+\bullet}$: 364.1132, found: 364.1131.

Optical rotation: $[\alpha]_D^{20}$= 31.2 (c 0.57, $CHCl_3$)



2*R*,4*S*,6*R*,8*R*-**87**

According to **Standard procedure D**, iodide 2*R*,4*S*,6*S*-**85** (104.1 mg, 0.30 mmol, dr>99:1, >99% *ee*) as a starting material (*R*)-propylene oxide (*R*-**82**) (70 μL, 0.90 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2Oc/^{i}hexane = 1/5 to afford 2*R*,4*S*,6*R*,8*R*-**87** (51.3 mg, 61% yield, dr(C(4)) = 99:1, >99% *ee*) as a colorless oil. The *ee* was determined using Mosher's ester analysis.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.37 – 7.30 (m, 4H), 7.29 – 7.24 (m, 1H), 4.60 (d, *J* = 11.8 Hz, 1H), 4.42 (d, *J* = 11.8 Hz, 1H), 3.88 (h, *J* = 6.3 Hz, 1H), 3.60 (dqd, *J* = 12.5, 6.1, 3.9 Hz, 1H), 1.86 – 1.74 (m, 1H), 1.70 – 1.56 (m, 2H), 1.44 – 1.38 (m, 1H), 1.38 – 1.22 (m, 3H), 1.19 (d, *J*

= 6.1 Hz, 3H), 1.17 (d, *J* = 6.3 Hz, 3H), 1.07 (ddd, *J* = 13.5, 9.2, 3.9 Hz, 1H), 0.97 (dt, *J* = 14.0, 7.2 Hz, 1H), 0.89 (d, *J* = 6.5 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H).

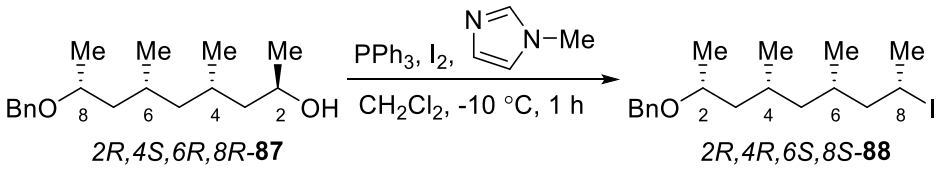
^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 139.3, 128.4, 127.8, 127.5, 72.7, 70.4, 66.5, 47.1, 45.9, 44.7, 27.4, 26.6, 23.7, 20.8, 20.5, 20.3.

MS (70 eV, EI) *m/z* (%): 260 (3) $[M\text{-}H_2O]^{+\bullet}$, 154 (5), 135 (4), 107 (5), 91 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3365 (w), 2963 (m), 2924 (m), 2870 (m), 1496 (w), 1454 (m), 1374 (m), 1342 (w), 1206 (w), 1123 (s), 1089 (m), 1064 (s), 1028 (s), 1010 (m), 974 (w), 951 (w), 938 (m), 916 (w), 871 (w), 834 (w), 790 (w), 733 (s), 696 (vs).

HRMS (EI) *m/z*: calcd for **$C_{18}H_{28}O^{+\bullet}$** $[M\text{-}H_2O]^{+\bullet}$: 260.2140, found: 260.2125.

Optical rotation: $[\alpha]_D^{20}$= -15.1 (c 0.46, $CDCl_3$)



2R,4S,6R,8R-**87** *2R,4R,6S,8S*-**88**

2*R*,4*R*,6*S*,8*S*-**88**

According to **Standard procedure B**, alcohol 2*R*,4*S*,6*R*,8*R*-**87** (90.0 mg, 0.32 mmol, dr(C(4))=99:1, >99% *ee*) as a starting material was used. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/100 to afford 2*R*,4*R*,6*S*,8*S*-**22** (100.1 mg, 80% yield, dr>99:1, >99% *ee*) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.37 – 7.31 (m, 4H), 7.30 – 7.26 (m, 1H), 4.61 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 4.27 – 4.16 (m, 1H), 3.61 (dqd, *J* = 8.9, 6.0, 3.9 Hz, 1H), 1.95 (d, *J* = 6.8 Hz, 3H), 1.94 – 1.88 (m, 1H), 1.84 – 1.71 (m, 2H), 1.62 (ddd, *J* = 13.6, 8.9, 4.4 Hz, 1H), 1.20 (d, *J* = 6.0 Hz, 3H), 1.25 – 1.16 (m, 1H), 1.14 – 0.99 (m, 3H), 0.85 (d, *J* = 5.7 Hz, 3H), 0.83 (d, *J* = 5.7 Hz, 3H).

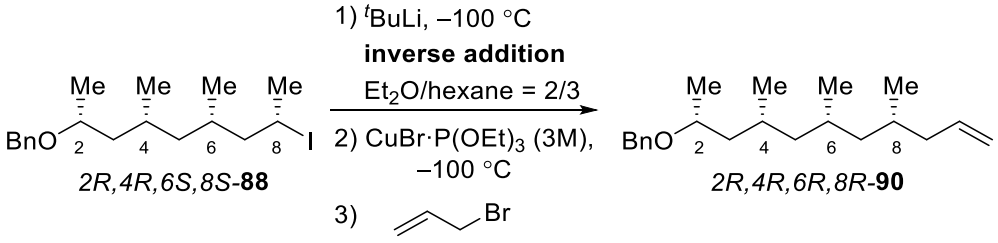
^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 139.2, 128.4, 127.8, 127.5, 72.8, 70.5, 49.7, 45.6, 45.0, 31.0, 30.2, 30.0, 26.4, 20.3, 20.0, 19.6.

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3030 (vw), 2962 (m), 2921 (m), 2867 (m), 1496 (w), 1453 (m), 1376 (m), 1342 (w), 1306 (w), 1262 (w), 1241 (w), 1207 (m), 1173 (m), 1161 (m), 1142 (m), 1124 (m),

1090 (m), 1067 (s), 1028 (m), 998 (w), 970 (w), 946 (w), 922 (w), 874 (w), 842 (w), 791 (w), 732 (s), 696 (vs).

HRMS (ESI) *m/z*: calcd for **$C_{18}H_{33}ONI^{+\bullet}$** $[M+NH_4]^{+\bullet}$: 406.1601, found: 406.1606.

Optical rotation: $[\alpha]_D^{20}$= 27.2 (c 0.50, $CHCl_3$)



2*R*,4*R*,6*R*,8*R*-**90**

According to **Standard procedure D**, iodide 2*R*,4*R*,6*S*,8*S*-**88** (78.8 mg, 0.20 mmol, dr=99:1) as a starting material and allyl bromide (52 μL, 0.60 mmol) as an electrophile were used. The crude product was purified by prep. HPLC using the *Chromolith SemiPrep RP-18e 100-10mm* column with 80-95% acetonitrile mixture and with speed 7.0 mL/min (retention time – 4.8 min) to afford 2*R*,4*R*,6*R*,8*R*-**90** (34.5 mg, 57% yield, dr(C(8))=97:3, >99% *ee*) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 7.37 – 7.22 (m, 4H), 5.78 (ddt, *J* = 17.2, 10.3, 7.1 Hz, 1H), 5.04 – 4.93 (m, 2H), 4.60 (d, *J* = 11.7 Hz, 1H), 4.42 (d, *J* = 11.7 Hz, 1H), 3.65 – 3.56 (m, 1H), 2.15 – 2.04 (m, 1H), 1.80 (tt, *J* = 13.7, 7.3 Hz, 2H), 1.70 – 1.51 (m, 4H), 1.28 – 1.10 (m, 6H), 1.04 (ddd, *J* = 13.5, 9.2, 4.0 Hz, 1H), 0.96 – 0.88 (m, 2H), 0.86 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.4 Hz, 3H), 0.81 (d, *J* = 6.6 Hz, 3H).

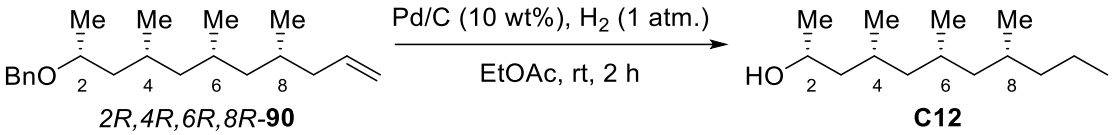
^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 139.3, 137.7, 128.4, 127.8, 127.5, 115.7, 72.8, 70.5, 46.0, 44.7, 44.7, 41.0, 30.1, 27.4, 26.6, 20.9, 20.6, 20.4, 20.3.

MS (70 eV, EI) *m/z* (%): 302 (2) $[M]^{+\bullet}$, 196 (3), 135 (18), 111 (13), 91 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3072 (w), 3032 (w), 2956 (s), 2915 (s), 2870 (m), 1719 (s), 1454 (m), 1377 (m), 1273 (s), 1160 (m), 1109 (vs), 1095 (s), 1069 (vs), 1027 (s), 993 (s), 974 (m), 948 (m), 909 (s), 804 (m), 733 (s), 711 (vs), 696 (s), 674 (m), 660 (m).

HRMS (EI) *m/z*: calcd for **$C_{21}H_{34}O^{+\bullet}$** $[M]^{+\bullet}$: 302.2604, found: 302.2610.

Optical rotation: $[\alpha]_D^{20}$= -12.8 (c 0.17, $CHCl_3$)



2R,4R,6R,8R-**90** **C12**

C12

To a solution of 2*R*,4*R*,6*R*,8*R*-**90** (19.9 mg, 65.8 µmol, dr(C(8))= 97:3, >99% *ee*) in EtOAc (10 mL) was added Pd/C (17.6 mg, 10% wt, 16 µmol) and the system was charged with a balloon of H_2 at room temperature. The reaction mixture was stirred for 2 h and then filtered through a pad of celite. The crude product was purified by column chromatography on silica gel with EtOAc/^{i}hexane = 1/10 to afford **C12** (13.0 mg, 92% yield, dr(C(8)) = 97:3, >99% *ee*) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 3.91 (dqd, *J* = 9.6, 6.1, 3.5 Hz, 1H), 1.71 (dpd, *J* = 10.7, 6.8, 3.8 Hz, 1H), 1.64 – 1.54 (m, 1H), 1.48 (ddd, *J* = 13.7, 9.5, 4.2 Hz, 2H), 1.43 – 1.22 (m, 4H), 1.20 (d, *J* = 6.1 Hz, 3H), 1.18 – 1.14 (m, 1H), 1.11 – 1.03 (m, 1H), 0.99 – 0.93 (m, 1H), 0.91 – 0.81 (m, 14H).

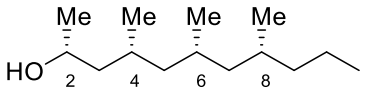
^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 65.9, 46.6, 46.0, 45.4, 39.0, 29.8, 27.3, 26.7, 24.6, 20.8, 20.6, 20.3, 20.1, 14.6.

MS (70 eV, EI) *m/z* (%): 199 (1) $[M\text{-}CH_3]^{+\bullet}$, 154 (8), 127 (6), 111 (71), 97 (18), 85 (49), 69 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3340 (w), 2957 (vs), 2920 (vs), 2872 (s), 2843 (m), 1459 (s), 1394 (w), 1377 (s), 1151 (m), 1114 (m), 1056 (m), 1000 (m), 972 (m), 958 (m), 941 (m), 926 (m), 895 (w), 853 (w), 837 (m), 806 (m), 762 (w), 738 (m), 722 (m), 704 (m), 672 (m), 666 (m), 658 (m).

HRMS (EI) *m/z*: calcd for **$C_{13}H_{27}O^{+\bullet}$** $[M\text{-}CH_3]^{+\bullet}$: 199.2062, found: 199.2062.

Optical rotation: $[\alpha]_D^{20}$= -12.4 (c 0.17, $CHCl_3$), lit.[109][130][105] $[\alpha]_D^{20}$= -12.3 (c 0.5, $CHCl_3$), $[\alpha]_D^{20}$= -12.8 (c 5.42, $CHCl_3$).

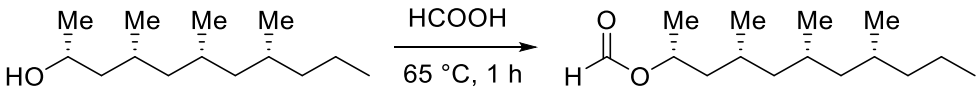


C12

Comparison with the literature values:

Reported chemical shifts[109] ^{13}C NMR, $CDCl_3$ (δ 77.0)	Obtained chemical shifts ^{13}C NMR, $CDCl_3$ (δ 77.16)
14.4	14.6
19.9	20.1
20.1	20.3
20.4	20.6
20.6	20.8
24.4	24.6
26.5	26.7
27.1	27.3
29.6	29.8
38.8	39.0
45.2	45.4
45.8	46.0
46.4	46.6
65.6	65.9

The other diastereomers are described in the literature.[131] The minor peaks correspond to the diastereomer at C(8).[131] The obtained analytical data of **C12** is identical to reported previously.[109][130][105]



C12 **70** (-)-lardolure

70 (-)-lardolure

A solution of **C12** (11.0 mg, 51.4 µmol, dr = 97:3, >99% *ee*) in HCOOH (0.50 mL) was stirred for 1 h at 65 ° C. After cooling to room temperature the reaction mixture was diluted with Et_2O and cautiously quenched with sat. aq. $NaHCO_3$. The phases were separated and the aq.

phase was extracted with Et_2O (3×5 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by column chromatography on silica gel with EtOAc/^{n}hexane = 1/40 to afford **70** (-)-lardolure (10.1 mg, 81% yield, dr>99:1, >99% *ee*) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: δ 8.06 (s, 1H), 5.16 (dddd, *J* = 9.8, 6.2, 3.6, 1.0 Hz, 1H), 1.71 (ddd, *J* = 13.8, 9.6, 4.0 Hz, 1H), 1.64 – 1.49 (m, 3H), 1.38 – 1.09 (m, 10H), 1.06 – 0.92 (m, 2H), 0.91 – 0.86 (m, 6H), 0.85 (d, *J* = 3.0 Hz, 3H), 0.83 (d, *J* = 2.9 Hz, 3H).

^{1}H NMR (800 MHz,C_6D_6) *δ*: 7.65 (s, 1H), 5.18 (dqd, *J* = 9.7, 6.2, 3.4 Hz, 1H), 1.68 – 1.58 (m, 3H), 1.56 – 1.50 (m, 1H), 1.40 – 1.29 (m, 3H), 1.28 – 1.21 (m, 2H), 1.16 (ddd, *J* = 13.6, 7.7, 5.9 Hz, 1H), 1.04 (d, *J* = 6.2 Hz, 3H), 0.91 (t, *J* = 7.1 Hz, 3H), 0.88 (m, 6H), 0.84 (d, *J* = 6.4 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 161.1, 69.3, 45.6, 45.5, 43.1, 39.1, 29.9, 27.4, 26.6, 21.1, 20.8, 20.5, 20.4, 20.1, 14.6.

^{13}C NMR (201 MHz, C_6D_6) *δ*: 160.3, 128.1, 68.5, 45.8, 45.7, 43.2, 39.3, 30.1, 27.6, 26.7, 21.0, 20.8, 20.6, 20.4, 20.4, 14.7.

MS (70 eV, EI) *m/z* (%): 196 (7) $[M\text{-}HCOOH]^{+\bullet}$, 153 (15), 127 (5), 111 (100), 97 (28), 85 (25), 69 (83).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2954 (s), 2922 (vs), 2869 (m), 2851 (m), 1728 (s), 1464 (m), 1461 (m), 1457 (m), 1378 (w), 1260 (m), 1183 (m), 1121 (m), 1095 (m), 1068 (m), 1062 (m), 1056 (m), 1018 (m), 801 (m).

HRMS (ESI$^-$) *m/z*: calcd for **$C_{13}H_{27}O^{+\bullet}$** $[M\text{-}H]^{+\bullet}$: 241.2173, found: 241.2172.

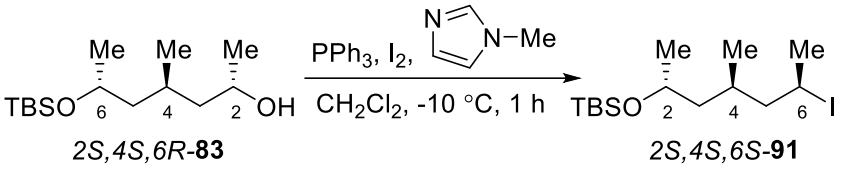
Optical rotation: $[\alpha]_D^{20}$= -3.3 (c 0.3, hexane), lit.[9,10,11] $[\alpha]_D^{20}$= -3.4 (c = 7.86, hexane)

Comparison with the literature values:

Reported chemical shifts[109] ^{13}C NMR, $CDCl_3$ (δ 77.0)	Obtained chemical shifts ^{13}C NMR, $CDCl_3$ (δ 77.16)	Obtained chemical shifts ^{13}C NMR, C_6D_6 (δ 128.06)
14.4	14.6	14.7
19.2	20.1	20.4
20.2	20.4	20.4

20.3	20.5	20.6
20.5	20.8	20.8
20.9	21.1	21.0
26.4	26.6	26.7
27.1	27.4	27.6
29.1	29.9	30.1
38.8	39.1	39.3
42.9	43.1,	43.2
45.2	45.5	45.7
45.4	45.6	45.8
69.0	69.3	68.5
160.9	161.1	160.3

The obtained analytical data is identical to reported previously.[109][130][105]



2S,4S,6R-**83** *2S,4S,6S*-**91**

2*S*,4*S*,6*S*-**91**

According to **Standard procedure B**, alcohol *2S,4S,6R*-**83** (0.56 g, 2.15 mmol, dr>99:1, >99% *ee*) as a starting material was used. The crude product was purified by column chromatography on silica gel with EtOAc/^{i}hexane = 1/100 to afford 2*S*,4*S*,6*S*-**91** (0.66 g, 83% yield, dr>99:1, >99% *ee*) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 4.25 – 4.14 (m, 1H), 3.88 (h, *J* = 6.2 Hz, 1H), 1.99 – 1.91 (m, 1H), 1.94 (d, *J* = 6.7 Hz, 3H), 1.78 – 1.66 (m, 1H), 1.46 – 1.30 (m, 2H), 1.21 – 1.15 (m, 1H), 1.13 (d, *J* = 6.2 Hz, 3H), 0.89 (s, 9H), 0.85 (d, *J* = 6.6 Hz, 3H), 0.08 (s, 3H), 0.06 (s, 3H).

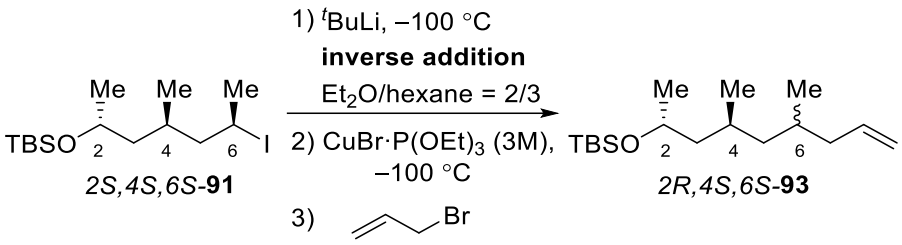
^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 66.9, 50.5, 47.4, 30.8, 29.7, 29.2, 26.1, 23.9, 19.1, 18.3, -4.1, -4.3.

MS (70 eV, EI) *m/z* (%):313 (5) [M- *t*Bu]$^{+\bullet}$, 243 (2), 229 (100), 185 (50), 159 (19), 75 (42), 69 (49).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2957 (m), 2927 (m), 2892 (m), 2886 (m), 2857 (m), 1472 (w), 1462 (m), 1446 (w), 1378 (m), 1361 (w), 1255 (m), 1175 (w), 1158 (m), 1126 (m), 1077 (m), 1045 (m), 1018 (w), 1006 (m), 991 (m), 957 (w), 880 (w), 833 (vs), 805 (m), 773 (vs), 724 (m), 715 (w), 663 (w).

HRMS (EI) *m/z*: calcd for **$C_{14}H_{30}OISi^{+\bullet}$** [M]$^{+\bullet}$: 369.1183, found: 369.1111.

Optical rotation: $[\alpha]_D^{20}$= -48.0 (c 1.00, $CHCl_3$)



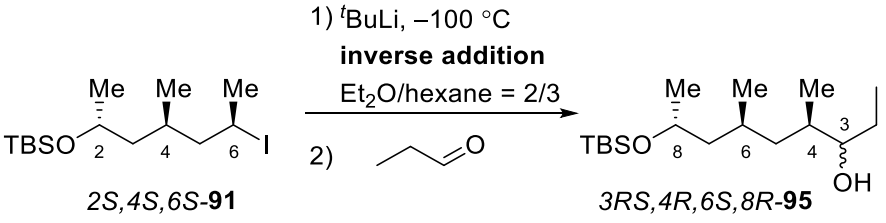
2*S*,4*S*,6*S*-**93**

According to **Standard procedure D**, iodide 2*S*,4*S*,6*S*-**91** (111.1 mg, 0.30 mmol, dr = 99:1) as a starting material and allyl bromide (78 μL, 0.90 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with *i*hexane to afford 2*S*,4*S*,6*S*-**93** (57.0 mg, 67% yield, dr (C(6))=85:15, >99% *ee*) as a colorless oil. The reported analytical data correspond to two diastereomers at C(6) in ratio 85:15.

^{1}H-NMR (400 MHz, $CDCl_3$) δ: 5.77 (ddt, *J* = 17.4, 10.6, 7.2 Hz, 1H), 5.03 – 4.95 (m, 2H), 3.92 – 3.81 (m, 1H), 2.13 – 2.03 (m, 1H), 1.87 – 1.76 (m, 1H), 1.67 – 1.48 (m, 2H), 1.46 – 1.30 (m, 1H), 1.29 – 1.20 (m, 2H), 1.11 (d, *J* = 6.0 Hz, 3H), 1.00 – 0.91 (m, 1H), 0.88 (s, 9H), 0.87 – 0.83 (m, 6H), 0.05 (s, 6H).

^{13}C-NMR (101 MHz, $CDCl_3$, *major diastereomer***) δ:** 137.8, 115.7, 67.2, 47.4, 45.4, 41.4, 30.0, 27.3, 26.1, 23.6, 20.7, 20.0, 18.4, -4.2, -4.5.

^{13}C-NMR (101 MHz, $CDCl_3$, *minor diastereomer***) δ:** 137.5, 115.9, 66.8, 47.0, 45.4, 41.4, 29.5, 27.3, 26.1, 24.0, 20.7, 20.1, 18.3, -4.1, -4.6.



3*RS*,4*R*,6*S*,8*R*-**95**

According to **Standard procedure C**, iodide 2*S*,4*S*,6*S*-**91** (111.2 mg, 0.30 mmol, dr > 99:1, >99% *ee*) as a starting material propionaldehyde (65 μL, 0.90 mmol) as an electrophile were used. The crude product was purified by column chromatography on silica gel with Et_2O/*i*-

hexane = 1/5 to afford 3*RS*,4*R*,6*S*,8*R*-**95** (56.3 mg, 62% yield, dr(C(4))=99:1, dr(C(3))=1:1, >99% *ee*) as a colorless oil. The reported analytical data correspond to two diastereomers at C(3) in ratio 1:1.

^{1}H-NMR (400 MHz, $CDCl_3$, *two diastereomers at C(3)***) δ:** 3.94 – 3.83 (m, 2H), 3.40 (td, *J* = 6.5, 3.4 Hz, 1H), 3.37 – 3.32 (m, 1H), 1.72 – 1.58 (m, 2H), 1.56 – 1.30 (m, 12H), 1.28 – 1.15 (m, 2H), 1.12 (d, *J* = 6.1 Hz, 3H), 1.11 (d, *J* = 6.0 Hz, 3H), 1.09 – 0.99 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H), 0.94 (t, *J* = 7.3 Hz, 3H), 0.91 – 0.86 (m, 27H), 0.83 (d, *J* = 6.8 Hz, 3H), 0.06 – 0.04 (m, 12H).

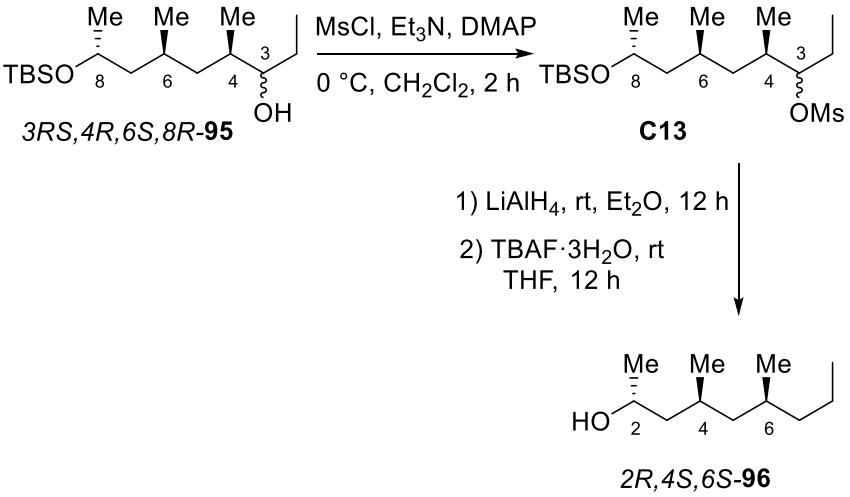
^{13}C-NMR (101 MHz, $CDCl_3$, *two diastereomers at C(3)***) δ:**77.9, 76.6, 67.4, 67.4, 46.9, 46.5, 42.0, 40.5, 35.8, 34.7, 27.6, 27.6, 27.3, 26.2, 26.1, 23.5, 23.3, 21.4, 21.0, 18.4, 15.8, 13.6, 10.8, 10.6, -4.3, -4.3, -4.5.

MS (70 eV, EI) *m/z* (%): 245 (7) [M- *t*Bu]$^{+\bullet}$, 171 (7), 159 (41), 133 (10), 120 (8), 111 (75), 97 (61), 83 (72), 75 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3353 (w), 2959 (vs), 2930 (vs), 2884 (m), 2857 (s), 1472 (m), 1463 (m), 1378 (m), 1255 (m), 1158 (w), 1127 (m), 1074 (s), 1049 (m), 1007 (m), 984 (m), 973 (m), 896 (w), 875 (w), 835 (vs), 807 (m), 774 (s), 742 (w), 676 (w).

HRMS (EI) *m/z*: calcd for **$C_{16}H_{35}O_2Si^{+\bullet}$** [M-$CH_3$]$^{+\bullet}$: 287.2406, found: 287.2388.

Optical rotation: $[\alpha]_D^{20}$= 27.2 (c 1.05, $CHCl_3$)



3RS,4R,6S,8R-**95**

C13

2R,4S,6S-**96**

2*R*,4*S,*6*S*-**96**

To a solution of alcohol 3*RS*,4*R,*6*S,*8*R*-**95** (250 mg, 0.83 mmol, >99% *ee*), Et_3N (0.69 mL, 4.98 mmol) and DMAP (101 mg, 0.83 mmol) in CH_2Cl_2 (5 mL) was added MsCl (0.13 mL, 1.66 mmol) at 0 °C dropwise. The reaction mixture was stirred for 2 h at 0 °C. Then the reaction mixture was carefully quenched with sat. aq. $NaHCO_3$ solution. The reaction mixture was extracted with CH_2Cl_2 (3×25 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The obtained crude **C13** product was used in the next step without any additional purification.

Tosylation was also performed, but in similar reaction conditions conversion of 3*RS*,4*R,*6*S,*8*R*-**29** was not full and side products were formed.

To a solution of compound **C13** in Et_2O (7 mL) was added $LiAlH_4$ (126 mg, 3.32 mmol) in one portion at 0 °C. The resulting reaction mixture was warmed to room temperature and stirred for 12 h. Then the reaction mixture was cooled to 0 °C and quenched with $Na_2SO_4 \cdot 10H_2O$. The resulting white powder was filtered off and washed with Et_2O (3×10 mL). The filtrate was evaporated. The obtained crude product **C13a** was used in the next step without any additional purification.

To a solution of compound **C13a** in THF (15 mL) was added $TBAF \cdot 3H_2O$ (1.05 g, 3.32 mmol) and the resulting reaction mixture was stirred for 12 h. Then the reaction mixture was quenched with water. The reaction mixture was extracted with Et_2O (3×30 mL). The combined organic phases were dried over $MgSO_4$ and the solvents were evaporated. The crude product was purified by column chromatography on silica gel with Et_2O/^{n}pentane = 1/6 to afford 2*R*,4*S,*6*S*-**96** (125 mg, 88% yield over 3 steps, dr>99:1, >99% *ee*) as a colorless oil. The *ee* was determined using Mosher's ester analysis

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 3.90 (m, 1H), 1.64 – 1.55 (m, 1H), 1.55 – 1.43 (m, 2H), 1.41 – 1.20 (m, 6H), 1.18 (d, *J* = 6.1 Hz, 3H), 1.08 – 0.98 (m, 1H), 0.97 – 0.91 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H).

^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 66.5, 47.2, 45.5, 39.1, 29.8, 27.5, 23.7, 20.8, 20.4, 20.1, 14.6.

MS (70 eV, EI) *m/z* (%): 157 (2) $[M\text{-}CH_3]^{+\bullet}$, 112 (11), 111 (44), 97 (9), 85 (42), 69 (100), 55 (23).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 3330 (m), 2958 (vs), 2924 (s), 2872 (s), 2846 (m), 1458 (s), 1378 (s), 1152 (m), 1116 (m), 1084 (w), 1056 (m), 1026 (m), 1006 (m), 970 (w), 948 (m), 924 (m), 876 (w), 856 (w), 834 (m), 810 (w), 772 (w), 764 (w), 738 (m), 720 (w), 688 (m), 664 (m).

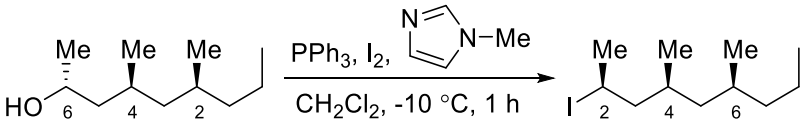
HRMS (EI) *m/z*: calcd for $\mathbf{C_{10}H_{21}O^{+\bullet}}$ $[M\text{-}CH_3]^{+\bullet}$: 157.1592, found: 157.1586.

Optical rotation: $[\alpha]_D^{20}$= -7.9 (c 0.68, $CHCl_3$)

Comparison with the literature values:

Reported chemical shifts[131] ^{13}C NMR, $CDCl_3$ (δ 77.0)	Obtained chemical shifts ^{13}C NMR, $CDCl_3$ (δ 77.16)
14.4	14.6
20.0	20.1
20.3	20.4
20.7	20.8
23.6	23.7
27.4	27.5
29.7	29.8
39.0	39.1
45.3	45.5
47.1	47.2
66.4	66.5

The other diastereomers are described in the literature.[131] The obtained analytical data of 2*R*,4*S*,6*S*-**30** is identical to reported previously.[131] The other diastereomers are described in the literature[131] and careful comparison of the data showed that only one diastereomer is obtained 2*R*,4*S*,6*S*-**96**.



2R,4S,6S-**96** *2S,4S,6S*-**97**

2*S*,4*S*,6*S*-**97**

According to **Standard procedure B**, alcohol 2*R*,4*S*,6*S*-**96** (121 mg, 0.70 mmol, dr>99:1, >99% *ee*) as a starting material was used. The crude product was purified by column chromatography on silica gel with ^{n}hexane to afford 2*S*,4*S*,6*S*-**97** (158 mg, 80% yield, dr>99:1, >99% *ee*) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 4.22 (dqd, *J* = 10.5, 6.7, 3.7 Hz, 1H), 1.95 (d, *J* = 6.7 Hz, 3H), 1.95 – 1.88 (m, 1H), 1.81 – 1.68 (m, 1H), 1.55 – 1.45 (m, 1H), 1.40 – 1.17 (m, 4H), 1.12 – 0.98 (m, 3H), 0.91 – 0.86 (m, 6H), 0.83 (d, *J* = 6.5 Hz, 3H).

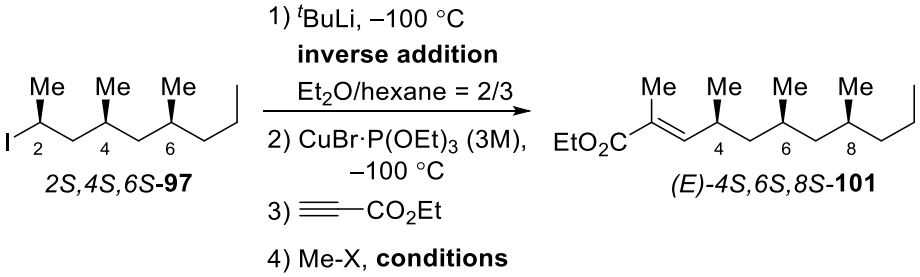
^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 49.9, 45.1, 39.5, 31.1, 30.2, 29.9, 29.6, 20.2, 20.1, 19.6, 14.6.

MS (70 eV, EI) *m/z* (%): 155 (35) $[M\text{-}I]^{+\bullet}$, 127 (7), 113 (15), 85 (100), 71 (85), 57 (85).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2958 (m), 2923 (m), 2853 (w), 1632 (w), 1457 (w), 1378 (w), 1258 (s), 1210 (w), 1174 (w), 1086 (s), 1012 (s), 864 (m), 792 (vs), 720 (m), 700 (m), 661 (m).

HRMS (EI) *m/z*: calcd for **$C_{11}H_{22}I^{+\bullet}$** $[M\text{-}H]^{+\bullet}$: 281.0766, found: 281.0511.

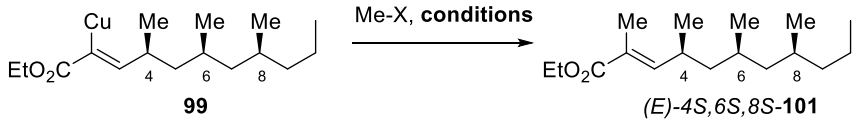
Optical rotation: $[\alpha]_D^{20}$= -33.3 (c 0.23, $CHCl_3$)



(*E*)-4*S*,6*S*,8*S*-**101**

According to **Standard procedure D**, iodide 2*S*,4*S*,6*S*-**97** (40.0 mg, 0.14 mmol, dr > 99:1) as a starting material and ethyl propiolate (22 μL, 0.21 mmol) as an electrophile were used. The reaction mixture was stirred for 3 min at –100 °C and turned red. Then the solvent was changed or another electrophile was added. The different conditions for the step 4 are summarized in the following Table 6.

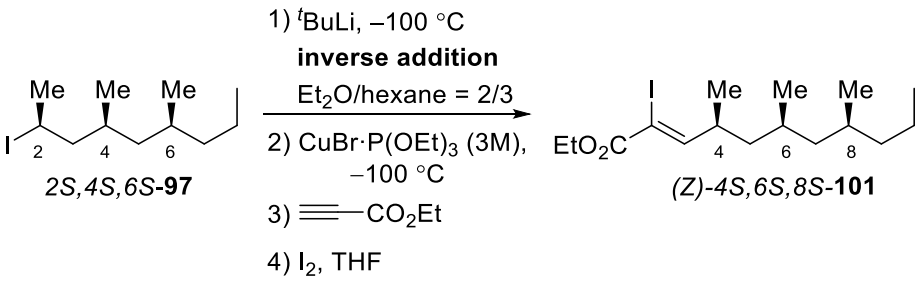
Table 6. Optimization of the reaction conditions.



99 *(E)-4S,6S,8S*-**101**

Entry	Me-X (3.0 equiv.)	Solvent	Temperature	Time	GC-yield of **35**
1	MeI	Et_2O/hexane	– 100 °C	1 h	0%
2	MeI	Et_2O/hexane	– 50 °C	1 h	0%
3	MeI	Et_2O/hexane	0 °C	1 h	0% (decomposition of **33**)
4	MeI	THF	– 100 °C	1 h	0%
5	MeI	THF	– 50 °C	1 h	0%
6	MeI	THF	0 °C	1 h	traces
7	MeI	THF	0 °C	30 h	40% (according to **33**)
8	$(MeO)_2SO_2$	Et_2O/hexane	– 100 °C	1 h	0%
9	$(MeO)_2SO_2$	Et_2O/hexane	– 50 °C	1 h	0%
10	$(MeO)_2SO_2$	Et_2O/hexane	0 °C	1 h	0% (decomposition of **33**)
11	$(MeO)_2SO_2$	THF	– 100 °C	1 h	0%
12	$(MeO)_2SO_2$	THF	– 50 °C	1 h	0%
13	$(MeO)_2SO_2$	THF	0 °C	1 h	traces
14	$(MeO)_2SO_2$	THF	0 °C	30 h	50% (according to **33**)
15	MeOTf	Et_2O/hexane	0 °C	1 h	0% (decomposition of **33**)
16	MeOTf	THF	0 °C	30 h	48% (according to **33**)

The best conditions (entry 14) allowed to obtain the product (*E*)-4*S*,6*S*,8*S*-**101** in 28% isolated yield (10.4 mg).



(*Z*)-4*S*,6*S*,8*S*-**100**

According to **Standard procedure D**, iodide 2*S*,4*S*,6*S*-**97** (40.0 mg, 0.14 mmol, dr > 99:1) as a starting material and ethyl propiolate (22 μL, 0.21 mmol) as an electrophile were used. The reaction mixture was stirred for 3 min at –100 °C and turned red. Then a solution of I_2 (107.1 mg, 0.42 mmol) in THF (0.40 mL) was added. The resulting reaction mixture was warmed to –50 °C and stirred for another 15 min. Then the reaction mixture was warmed to 0 °C and stirred for 10 min until it turned pale yellow. After standard work-up, the crude product was purified by column chromatography on silica gel with Et_2O/*n*hexane = 70:1 to afford (*Z*)-4*S*,6*S*,8*S*-**100** (30.5 mg, 57% yield, dr>99:1, *E/Z* =1:99, >99% *ee*) as a colorless oil. The iodide (*Z*)-4*S*,6*S*,8*S*-**100** slowly isomerizing under light.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 6.91 (d, *J* = 9.5 Hz, 1H), 4.26 (qd, *J* = 7.1, 3.1 Hz, 2H), 2.81 – 2.68 (m, 1H), 1.55 – 1.43 (m, 2H), 1.42 – 1.30 (m, 1H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.30 – 1.08 (m, 6H), 1.02 (d, *J* = 6.7 Hz, 3H), 0.98 – 0.90 (m, 1H), 0.90 – 0.85 (m, 6H), 0.81 (d, *J* = 6.6 Hz, 3H).

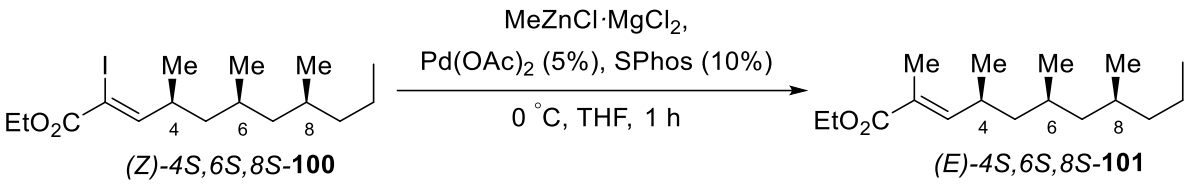
^{13}C-NMR (101 MHz, $CDCl_3$) *δ*: 163.2, 158.6, 93.5, 62.8, 45.6, 43.5, 39.7, 39.4, 29.8, 28.5, 20.9, 20.1, 19.5, 14.6, 14.3.

MS (70 eV, EI) *m/z* (%): 335 (1) $[M\text{-}OEt]^{+\bullet}$, 253 (28), 239 (14), 227 (89), 225 (41), 199 (100), 179 (51), 155 (12), 137 (11), 123 (28), 109 (53), 95 (86), 81 (15), 69 (29).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2957 (m), 2925 (m), 2870 (m), 1714 (s), 1612 (w), 1457 (m), 1378 (m), 1366 (m), 1300 (w), 1242 (vs), 1225 (s), 1203 (s), 1159 (m), 1142 (m), 1094 (m), 1037 (s), 970 (m), 952 (m), 896 (w), 864 (m), 843 (m), 802 (s), 750 (s), 685 (m), 665 (m).

HRMS (EI) *m/z*: calcd for **$C_{14}H_{24}OI^{+\bullet}$** $[M\text{-}OEt]^{+\bullet}$: 335.0872, found: 335.0865.

Optical rotation: $[\alpha]_D^{20}$= 5.3 (c 0.64, $CHCl_3$)



(Z)-4S,6S,8S-**100** *(E)-4S,6S,8S*-**101**

(*E*)-4*S*,6*S*,8*S*-**101**

$MeZnCl \cdot MgCl_2$ was prepared by mixing $ZnCl_2$ solution (0.5 M in THF, 1.0 equiv.) and MeMgCl (2.8 M, 1.05 equiv.) at 0 °C. The obtained solution was titrated with I_2 and the final concentration of $MeZnCl \cdot MgCl_2$ is 0.38 M. To a mixture of (*Z*)-4*S*,6*S*,8*S*-**100** (20.2 mg, 53.1 µmol), SPhos (2.2 mg, 5.3 µmol) and $Pd(OAc)_2$ (0.6 mg, 3.7 µmol) in THF (1.00 mL) was added and the solution of at $MeZnCl \cdot MgCl_2$ (182 µL, 0.38 M in THF, 70.0 µmol) at 0 °C using syringe pump (flow = 1.0 mL/h). After addition, the reaction mixture was stirred for another 1 h. The reaction mixture was diluted with Et_2O and quenched with few drops of sat. aq. NH_4Cl solution. The obtained mixture was passed through a plug of $MgSO_4$. The filtrate was evaporated. The crude product was purified by column chromatography on silica gel with Et_2O/^{i}hexane = 1/30 to afford (*E*)-4*S*,6*S*,8*S*-**101** (11.7 mg, 82% yield, dr>99:1, *E/Z* > 99:1 >99% *ee*) as a colorless oil.

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 6.50 (dq, *J* = 10.2, 1.4 Hz, 1H), 4.25 – 4.12 (m, 2H), 2.69 – 2.54 (m, 1H), 1.85 (d, *J* = 1.4 Hz, 3H), 1.53 – 1.43 (m, 1H), 1.42 – 1.12 (m, 6H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.11 – 1.00 (m, 2H), 0.98 (d, *J* = 6.7 Hz, 3H), 0.95 – 0.88 (m, 1H), 0.87 (t, *J* = 7.2 Hz, 3H), 0.83 – 0.79 (m, 6H).

^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 168.6, 148.4, 126.4, 60.5, 45.7, 44.4, 39.4, 31.0, 29.7, 28.2, 20.8, 20.6, 20.1, 14.6, 14.4, 12.6.

MS (70 eV, EI) *m/z* (%): 268 (2) $[M]^{+\bullet}$, 223 (8), 183 (15), 179 (12), 155 (11), 142 (11), 127 (21), 115 (86), 111 (29), 102 (24), 95 (21), 87 (100), 83 (55), 69 (52).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2957 (m), 2927 (m), 2872 (m), 2846 (w), 1712 (vs), 1650 (w), 1458 (m), 1378 (m), 1367 (m), 1309 (m), 1272 (m), 1261 (s), 1226 (m), 1205 (m), 1150 (m), 1101 (s), 1034 (m), 970 (w), 934 (w), 867 (w), 803 (m), 750 (s), 701 (w), 686 (w), 679 (w).

HRMS (EI) *m/z*: calcd for $C_{17}H_{32}O_2^{+\bullet}$ $[M]^{+\bullet}$: 268.2397, found: 268.2396.

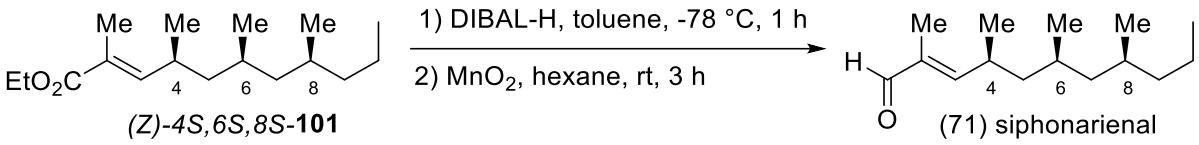
Optical rotation: $[\alpha]_D^{20}$= 19.3 (c 0.60, $CHCl_3$), lit.[13,14] $[\alpha]_D^{20}$= 19.8 (c 0.43, $CHCl_3$), $[\alpha]_D^{20}$= 18.1 (c 0.9, $CHCl_3$).

Comparison with the literature values:

Reported chemical shifts[112,113] ^{1}H NMR, $CDCl_3$ (δ 7.26)	Obtained chemical shifts ^{1}H NMR, $CDCl_3$ (δ 7.26)
6.51 (dd, *J* = 10.2, 1.4 Hz, 1 H)	6.50 (dq, *J* = 10.2, 1.4 Hz, 1H)
4.19 (m, 2H)	4.25 – 4.12 (m, 2H)
2.62 (m, 1 H)	2.69 – 2.54 (m, 1H)
1.86 (d, *J* = 1.4 Hz, 3 H)	1.85 (d, *J* = 1.4 Hz, 3H)
	1.53 – 1.43 (m, 1H)
	1.42 – 1.12 (m, 6H)
1.30 (t, *J* = 7.2 Hz, 3 H)	1.29 (t, *J* = 7.1 Hz, 3H)
	1.11 – 1.00 (m, 2H)
0.99 (d, *J* = 6.6 Hz, 3 H)	0.98 (d, *J* = 6.7 Hz, 3H)
	0.95 – 0.88 (m, 1H)
0.88 (d, *J* = 7.2 Hz, 3 H)	0.87 (t, *J* = 7.2 Hz, 3H)
0.83 (d, *J* = 5.5 Hz, 3 H)	0.83 – 0.79 (m, 6H)
0.81 (d, *J* = 6.5 Hz, 3 H)	

Reported chemical shifts[112,113] ^{13}C NMR, $CDCl_3$ (δ 77.0)	Obtained chemical shifts ^{13}C NMR, $CDCl_3$ (δ 77.16)
12.47	12.64
14.27	14.43
14.39	14.56
19.97	20.13
20.43	20.58
20.62	20.78
28.08	28.22
29.59	29.74
29.70	
30.86	31.01
39.29	39.44
44.30	44.44
45.56	45.71
60.34	60.51
126.2	126.35
148.2	148.39
168.4	168.62

The obtained analytical data of (*E*)-4*S*,6*S*,8*S*-**101** is identical to reported previously.[112,113]



(Z)-4S,6S,8S-**101** (**71**) siphonarienal

The reactions were performed according to the literature.[112,113] **Warning:** the aldehyde siphonarienal (**71**) is easily oxidized to the corresponding acid[114] under air (NMR spectra are shown in the next part below). Siphonarienal (**71**) (3.7 mg) was obtained in 80% yield from (*E*)-4*S*,6*S*,8*S*-**101** (5.6 mg, 20.9 µmol).

^{1}H-NMR (400 MHz, $CDCl_3$) *δ*: 9.40 (s, 1H), 6.22 (dd, *J* = 10.1, 1.3 Hz, 1H), 2.92 – 2.73 (m, 1H), 1.77 (d, *J* = 1.3 Hz, 3H), 1.40 – 1.14 (m, 9H), 1.05 (d, *J* = 6.7 Hz, 3H), 0.98 – 0.92 (m, 1H), 0.87 (t, *J* = 7.3 Hz, 3H), 0.84 (d, *J* = 6.5 Hz, 3H), 0.80 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (101 MHz, $CDCl_3$) *δ*: 195.8, 161.0, 138.1, 45.7, 44.3, 39.4, 31.4, 29.8, 28.4, 20.7, 20.5, 20.2, 20.1, 14.5, 9.5.

MS (70 eV, EI) *m/z* (%): 224 (1) $[M]^{+\bullet}$, 206 (2), 191 (15), 151 (26), 140 (26), 123 (47), 111 (56), 98 (72), 83 (40), 69 (100).

IR (ATR) $\tilde{\nu}$ (cm^{-1}): 2960 (w), 2922 (m), 2852 (w), 1695 (w), 1633 (w), 1466 (w), 1458 (w), 1412 (w), 1378 (w), 1259 (s), 1085 (s), 1014 (vs), 864 (m), 794 (vs), 701 (m), 662 (m).

HRMS (EI) *m/z*: calcd for **$C_{15}H_{28}O^{+\bullet}$** $[M]^{+\bullet}$: 224.2135, found: 224.2131.

Optical rotation: $[\alpha]_D^{20}$= 16.2 (c 0.09, $CHCl_3$), lit.[13,14,16] $[\alpha]_D^{20}$= 19.8 (c 0.43, $CHCl_3$), $[\alpha]_D^{25}$= 16.1 (c 1.1, $CHCl_3$), $[\alpha]_D^{22}$= 16.1 (c 1.1, $CHCl_3$).

Comparison with the literature values:

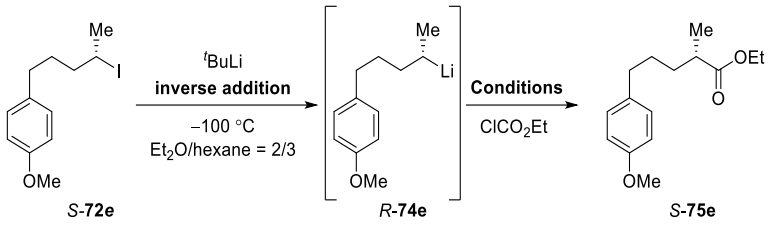
Reported chemical shifts[112,113] ^{1}H NMR, $CDCl_3$ (δ 7.26)	Obtained chemical shifts ^{1}H NMR, $CDCl_3$ (δ 7.26)
9.40 (s, 1H)	9.40 (s, 1H)
6.22 (dd, *J* = 10.1, 1.2 Hz, 1H)	6.22 (dd, *J* = 10.1, 1.3 Hz, 1H)
2.84 (m, 1H)	2.92 – 2.73 (m, 1H)
1.78 (d, *J* = 1.2 Hz, 3H)	1.77 (d, *J* = 1.3 Hz, 3H)
	1.40 – 1.14 (m, 9H)
1.05 (d, *J* = 6.7 Hz, 3H)	1.05 (d, *J* = 6.7 Hz, 3H)
	0.98 – 0.92 (m, 1H)
0.88 (t, *J* = 7.0 Hz, 3H)	0.87 (t, *J* = 7.3 Hz, 3H)
0.84 (d, *J* = 6.5 Hz, 3H)	0.84 (d, *J* = 6.5 Hz, 3H)
0.81 (d, *J* = 6.6 Hz, 3H)	0.80 (d, *J* = 6.6 Hz, 3H)

Reported chemical shifts[13,14] ^{13}C NMR, $CDCl_3$ (δ 77.0)	Reported chemical shifts[132] ^{13}C NMR, $CDCl_3$ (δ 77.03)	Obtained chemical shifts ^{13}C NMR, $CDCl_3$ (δ 77.16)
9.37	9.4	9.54
14.38	14.4	14.54
19.98	20.0	20.15
20.02	20.0	20.18
20.32	20.3	20.47
20.53	20.5	20.70
28.21	28.2	28.36
29.61	29.6	29.75
31.23	31.2	31.38
39.22	39.2	39.38
44.19	44.2	44.33
45.56	45.6	45.71
138.0	138.0	138.11
160.8	160.8	161.02
195.6	195.6	195.83

The obtained analytical data of siphonarienal (**71**) is identical to reported previously.[112,113]

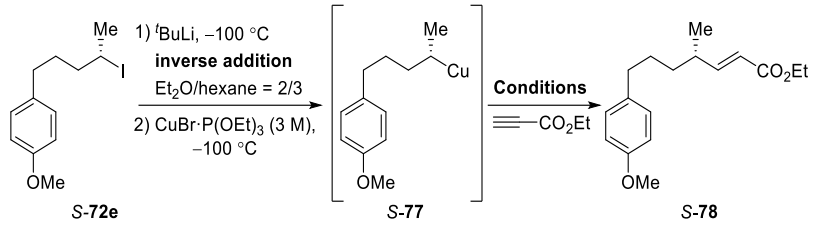
Configurational stability study

Table 7 Study of the configurational stability of *R*-**74e** at different temperatures.



Entry	Temperature	Time	*ee* and GC-yield
1	– 100 °C	2 min	92.0% *ee* and 64% GC-yield (61% isolated yield)
2	– 100 °C	10 min	86.2% *ee* and 57% GC-yield
3	– 80 °C	10 min	36.4% *ee* and 54% GC-yield
4	– 60 °C	10 min	2.0% *ee* and 50% GC-yield
5	– 40 °C	10 min	0% *ee* and 27% GC-yield
6	– 20 °C	10 min	0% *ee* and 19% GC-yield
7	0 °C	10 min	0% *ee* and 13% GC-yield

Table 8. Study of the configurational stability of *S*-**77** at different temperatures.



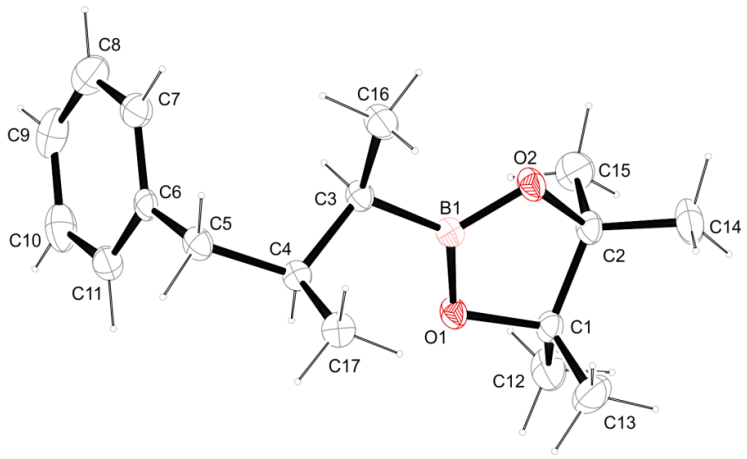
S-**72e** *S*-**77** *S*-**78**

Entry	Temperature	Time	*ee* and GC-yield
1	– 100 °C	1 min	92.2% *ee* and 54% GC-yield (47% isolated yield)
2	– 100 °C	10 min	92.0% *ee* and 53% GC-yield
3	– 80 °C	10 min	92.0% *ee* and 51% GC-yield
4	– 60 °C	10 min	91.4% *ee* and 48% GC-yield
5	– 40 °C	10 min	88.6% *ee* and 45% GC-yield
6	– 20 °C	10 min	85.8% *ee* and 29% GC-yield
7	0 °C	10 min	decomposition

Appendix

X-Ray structures

X-ray crystal structure analysis of *syn*-59a



The data collection was performed on a Bruker D8Quest IμS diffractometer, using MoKα radiation at a measurement temperature of 173 K. The structure was solved by direct methods with SIR97[S12] and refined with SHELXL-97.[S13]All hydrogen atoms were added in ideal geometry riding on their parent atoms.

CCDC 1456695 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://summary.ccdc.cam.ac.uk/structure-summary-form.

[S12] A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori, R. Spagna, *J. Appl. Crystallogr.* **1999**, *32,* 115–119.

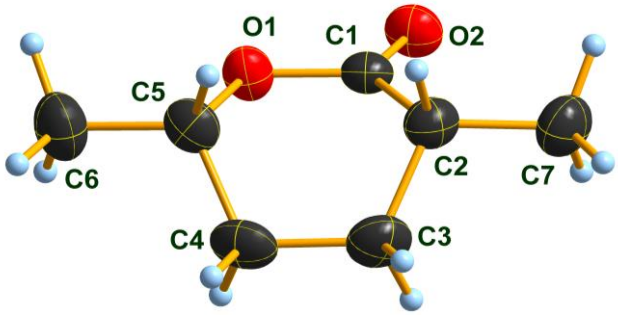
[S13] G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *64,* 112–122.

Sample, crystal, measurement and refinement details.

	***syn*-59a**
net formula	$C_{17}H_{27}BO_2$
M_r/g mol^{-1}	274.19
crystal size/mm	0.100 × 0.090 × 0.080
crystal system	monoclinic
space group	'P 21/n'
a/Å	9.1129(6)
b/Å	9.3053(7)
c/Å	19.6142(16)
α/°	90
β/°	91.088(2)
γ/°	90
V/Å^3	1663.0(2)
Z	4
calc. density/g cm^{-3}	1.095
μ/mm^{-1}	0.068
absorption correction	multi-scan
transmission factor range	0.8284–0.9579
refls. measured	27343
R_{int}	0.0751
mean σ(*I*)/*I*	0.0387
θ range	2.423–25.09
observed refls.	2124
x, y (weighting scheme)	0.0383, 0.4103
hydrogen refinement	constr
refls in refinement	2945
parameters	187
restraints	0
$R(F_{obs})$	0.0472
$R_w(F^2)$	0.1027
S	1.079
shift/error$_{max}$	0.001
max electron density/e Å^{-3}	0.139
min electron density/e Å^{-3}	−0.205

Appendix

X-ray crystal structure analysis of *lactone,* obtained from 2*R*,5*S*-57h



Single crystals of compound, suitable for X-ray diffraction, were obtained by slow evaporation of $CDCl_3$ solution. The crystals were introduced into perfluorinated oil and a suitable single crystal was carefully mounted on the top of a thin glass wire. Data collection was performed with an Oxford Xcalibur 3 diffractometer equipped with a Spellman generator (50 kV, 40 mA) and a Kappa CCD detector, operating with Mo-K_α radiation (λ = 0.71071 Å).

Data collection was performed with the CrysAlis CCD software;[a] CrysAlis RED software[b] was used for data reduction. Absorption correction using the SCALE3 ABSPACK multiscan method[c] was applied. The structures were solved with SHELXS-97,[d] refined with SHELXL-97[e] and finally checked using PLATON.[f]

CCDC-1817730 contains supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif

Appendix

Sample, crystal, measurement and refinement details.

Empirical formula	$C_7H_{12}O_2$
Formula mass	128.17
T[K]	173(2)
Crystal size [mm]	0.47 × 0.12 × 0.11
Crystal description	colorless rod
Crystal system	orthorhombic
Space group	$P2_12_12_1$
a [Å]	7.2488(6)
b [Å]	9.2592(6)
c [Å]	10.7523(6)
α [°]	90.0
β [°]	90.0
γ [°]	90.0
V [Å^3]	721.67(9)
Z	4
$\rho_{calcd.}$ [g cm^{-3}]	1.180
μ [mm^{-1}]	0.085
F(000)	280
Θ range [°]	4.38 – 25.24
Index ranges	$-7 \leq h \leq 9$
	$-12 \leq k \leq 12$
	$-14 \leq l \leq 13$
Reflns. collected	5970
Reflns. obsd.	1354
Reflns. unique	1783 (R_{int} = 0.0329)
R_1, wR_2 (2σ data)	0.0428, 0.0873
R_1, wR_2 (all data)	0.0639, 0.0980
GOOF on F^2	1.036
Peak/hole [e Å^{-3}]	0.148 / -0.162

Appendix

List of abbreviations

(*E*)	Entgegen (opposite, *trans*)
(*Z*)	Zusammen (together, *cis*)
Ac	Acetyl
aq.	Aqueous
(*S*)-*p*-tol-BINAP	(*S*)- 2,2'-Bis(di-p-tolylphosphino)-1,1'-binaphthyl
Boc	*tert*-Butyloxycarbonyl
^{n}Bu	*n*-Butyl
^{s}Bu	*sec*-Butyl
^{t}Bu	*tert*-Butul
br	Broad (NMR / IR)
Cp	Cyclopentadienyl anion ($C_5H_5^-$)
d	Dublett (NMR)
δ	Chemical shift
DCM	Dichloromethane
DEAD	Diethyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-(Dimethylamino)-pyridine
DMF	Dimethylformamide
dr	Diastereomeric ratio
ee	Enantiomeric excess
EA	Ethyl acetate (EtOAc)
EI	Electron impact
ESI	Electrospray ionization mass spectrometry
Et	Ethyl
Et_2O	Diethyl ether

Appendix

equiv.	Equivalents
g	Grams
h	Hours
HRMS	High resolution mass spectroscopy
IBAO	*Iso*-butylaluminoxane
IR	Infrared
J	Coupling constant
LAH	Lithium aluminium hydride ($LiAlH_4$)
LiDBB	4,4'-Di-*tert*-butylbiphenylide
LG	Leaving group
M	Molar (mol/L)
m	Multiplet (NMR), medium (IR, intensity between 60% and 40% of max. intensity)
Me	Methyl
MeOBpin	2-Methoxy-4,4,5,5-tetra-methyl-1,3,2-dioxaborolane
MeOH	Methanol
mg	Milligrams
min.	Minutes
mL	Millilitre
mp	Melting point
NMI	1-Methylimidazole
(-)-$(NMI)_2ZrCl_2$	(-)-Dichlorobis-(neomenthylindenyl)zirconium
NMR	Nuclear magnetic resonance
OAc	Acetate
p	Pentet (NMR)
Ph	Phenyl
PHMS	Polymethylhydrosiloxane

PG	Protecting group
ppm	Parts per million
Py	Pyridine
^{i}Pr	*iso*-Propyl
^{n}Pr	*n*-Propyl
q	Quartet (NMR)
R	(Organic) residue
rt	Room temperature
s	Singlet (NMR), strong (IR, between 60% and 80% of max. intensity)
sat.	Saturated
SET	Single electron transfer
sp	Sparteine
t	Triplet (NMR)
TBAF	Tetra-*n*-butylammonium fluoride ($^{n}Bu_4NF$)
TBS	*tert*–Butyl dimethyl silyl
Tf	Triflate (Trifluoromethanesulfyl)
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
vs	Very strong (IR, higher than 80% of max. intensity)
vw	Very weak (IR, below 20% of max. intensity)
w	Weak (IR, between 40% and 20% of max. intensity)
ZACA reaction	Zirconium-catalyzed asymmetric carbo-alumination reaction

Appendix

Curriculum Vitae

Varvara Morozova

Education

09/2014 – 04/2018 **Ludwig Maximilian University of Munich, Faculty of Chemistry and Pharmacy,** Munich, Germany
PhD student, Prof. Dr. Paul Knochel group, Summa Cum Laude (with highest honours)

- Developed a new methodology for constructing chiral molecules using chiral metalorganic species (organolithium, organocopper and organotitan) and applied the methodology for the total synthesis of a number of biologically active compounds in iterative fashion.
- Results were presented at three German Research Foundation (DFG) meetings and at OMCOS19 in Jeju, South Korea.

09/2014 – 06/2014 **Ludwig Maximilian University of Munich, Faculty of Chemistry and Pharmacy,** Munich, Germany
Diploma thesis, Prof. Dr. Herbert Mayr group

- Performed mechanistic studies of the hydride transfer in the hydrogenation reactions of electron-deficient C=C double bonds, catalyzed by frustrated Lewis pairs (FLPs) under H_2 pressure.
- Developed an alternative and H_2 free synthesis of different hydridoborates – intermediates of the hydrogenation reactions catalyzed by FLPs.

09/2009 – 06/2014 **Higher Chemical College of the Russian Academy of Sciences**,
(part of D. Mendeleyev University of Chemical Technology), Moscow, Russia
Dipl.-Chem., Graduated with honors, GPA = 4.99/5

Internships and part-time jobs

09/2014 – present **Ludwig Maximilian University of Munich, Faculty of Chemistry and Pharmacy,** Munich, Germany
Teaching assistant and research supervisor for students

10/2012 – 04/2013 **Innovative chemical engineering, LLC** (middle size chemical company), Moscow, Russia
Part-time Student

- In a collaboration with one of the biggest chemical company in Russia, was involved in the development of a new method of the separation of the rare-earth metals, which is now applied in the industrial process.
- Prepared few mini reviews on different chemical topics, which were used as a basis for several new directions.

09/2009 – 05/2013 **N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences,** Moscow, Russia
Part-time Student

- Investigated protonation reactions of alkenes in non-acidic media – 1,1,1,3,3,3-hexafluoro-2-propanol.

06–09/2012, 06–09/2011 **Ludwig Maximilian University of Munich, Faculty of Chemistry and Pharmacy,** Munich, Germany
Summer Internships, Prof. Dr. Herbert Mayr group

- Synthesized different aryltrifluoroborates and studied their reactivity towards various electrophiles..

06–09/2010 **Karlsruhe Institute of Technology, Institute of Organic Chemistry,** Karlsruhe, Germany
Summer Internship, Prof. Dr. Stefan Braese group

- Prepared azocompounds and studied their physical properties.

Appendix

Publications

G. Berionni, **V. Morozova**, M. Heininger, P. Mayer, P. Knochel, H. Mayr. Electrophilic aromatic substitutions of aryltrifluoroborates with retention of the BF3- group: quantification of the activating and directing effects of the trifluoroborate group. *J. Am. Chem. Soc.* **2013**, *135*, 6317. (Highlighted in *Synfacts*, **2013**, *9*, 723).

V. Morozova, P. Mayer, G. Berionni. Scope and Mechanisms of Frustrated Lewis Pair Catalyzed Hydrogenation Reactions of Electron-Deficient C=C Double Bonds. *Angew. Chem. Int. Ed.* **2015**, *54*, 14508.

V. Morozova, K. Moriya, P. Mayer, P. Knochel. Stereoselective Synthesis and Retentive Trapping of α-Chiral Secondary Alkyllithiums Leading to Stereodefined α,β-Dimethyl Carboxylic Esters. *Chem. Eur. J.* **2016**, *22*, 9962.

V. Morozova, J. Skotnitzki, K. Moriya, K. Karaghiosoff, P. Knochel. Preparation of Optically Enriched Secondary Alkyllithium and Alkylcopper Reagents. Synthesis of (-)-Lardolure and Siphonarienal. *Angew. Chem. Int. Ed.* **2018**, *57,* 5516.

J. Skotnitzki, **V. Morozova**, P. Knochel. Diastereoselective Copper-Mediated Cross-Couplings between Stereodefined Secondary Alkylcoppers with Bromoalkynes. *Org. Lett*. **2018**, *20*, 2365.

Awards and Honors

2012 *First Prize*, Mendeleev Competition of Chemistry Students (the biggest chemical student competition in Russia), St. Petersburg State Technological Institute, Saint-Petersburg

2012 *The award from Patent attorney And. L. Stoyachenko «For a non-standard solution of a scientific problem»*, Mendeleev Competition of Chemistry Students, St. Petersburg State Technological Institute, Saint-Petersburg

2009 Selected as a gifted high school student to represent Russia in the International Science Students Fair (ISSF), National Junior College, Singapore, Singapore

Languages

English – fluent, Russian – native, German – low intermediate, French – beginner.

Literature

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