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Cu-catalyzed enantioselective allylic alkylation with organolithium reagents

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This protocol describes a method for the catalytic enantioselective synthesis of tertiary and quaternary carbon stereogenic centers, which are widely present in pharmaceutical and natural products. The method is based on the direct reaction between organolithium compounds, which are cheap, readily available and broadly used in chemical synthesis, and allylic electrophiles, using chiral copper catalysts. The methodology involves the asymmetric allylic alkylation (AAA) of allyl bromides, chlorides and ethers with organolithium compounds using catalyst systems based on Cu–Taniaphos and Cu–phosphoramidites. The protocol contains a complete description of the reaction setup, a method based on ¹H-NMR, gas chromatography–mass spectrometry (GC–MS) and chiral HPLC for assaying the regioselectivity and enantioselectivity of the product, and isolation, purification and characterization procedures. Six Cu-catalyzed AAA reactions between different organolithium reagents and allylic systems are detailed in the text as representative examples of these procedures. These reactions proceed within 1–10 h, depending on the nature of the allylic substrate (bromide, chloride, or ether and disubstituted or trisubstituted) or the chiral ligand used (Taniaphos or phosphoramidite). However, the entire protocol, including workup and purification, generally requires an additional 4–7 h to complete.

INTRODUCTION

The synthesis of chiral structures is one of the key areas of the chemical sciences. Catalytic enantioselective C–C bond formation is a powerful approach that can be used to construct an enormous variety of chiral molecules. Cu-catalyzed AAA is among the most valuable and powerful methodologies for the preparation of chiral building blocks of prime interest for the synthesis of natural products and pharmaceuticals^{1–9}. This transformation generally leads to the S_N2'-functionalized product bearing a terminal olefin next to a carbon stereocenter, which can be further functionalized (Fig. 1a). Complementary to the well-studied Pd-catalyzed AAA, which usually uses soft and stabilized nucleophiles (Fig. 1b)^{10–12}, Cu-catalyzed AAA typically represents the most efficient catalytic process for the use of organometallic reagents, including organoaluminium, organozinc, organomagnesium, and organozirconium compounds. However, the use of cheap and readily available organolithium reagents had not been successfully applied in catalytic asymmetric C–C bond formation until recently^{13–18}. This protocol describes the application of organolithium compounds for the catalytic enantioselective C–C bond formation of tertiary and quaternary stereogenic centers.

Organolithium reagents are very versatile and are among the most widely used reagents in organic synthesis, with numerous applications in the preparation of polymers, pharmaceuticals and a range of other industrial products^{19–21}. Many organolithium compounds are commercially available and often are cheaper than the corresponding boron, tin, zinc or aluminum reagents. In addition, they often serve as precursors for the preparation of softer organometallic reagents and, therefore, their direct use would avoid the necessity for transmetalation (e.g., transmetalation with anhydrous ZnBr₂) or subsequent purification, as is the case in the preparation of boronic acids or tin compounds²².

We have reported for the first time that highly reactive organolithium reagents can be used in Cu-catalyzed AAA of allyl bromides with excellent regioselectivity and enantioselectivity using chiral ferrocenyl-based diphosphine ligand (Taniaphos)^{23,24} as a chiral ligand (Fig. 2a)¹³. The high reactivity of organolithium reagents can be tamed by the judicious choice of reaction conditions. The desired γ-substituted compounds (S_N2'-products) were obtained with high selectivity and without formation of side products. The corresponding organolithium reagent is generally diluted with *n*-hexane and added slowly to a solution of the catalyst and allyl halide or allyl ether in dichloromethane at –80 °C. The enantioselectivity of the reaction is independent of the copper salt used, although CuBr·SMe₂ yielded the highest regioselectivities. This catalytic system tolerates the presence of halides in the aromatic moieties of the allylic substrates without the presence of the common lithium–halogen exchange. Moreover, other functional groups that may react with organolithium reagents such as the benzyloxy-, *N*-Boc-protected amine-sensitive ester and highly sensitive ester groups are also tolerated, leading to the corresponding alkylated products in high regioselectivity and enantioselectivity¹³.

Figure 1 | Pd- and Cu-catalyzed AAA methodologies.

Figure 2 | Cu-catalyzed AAA using organolithium compounds; preferred chiral ligands for different combinations of allylic substrates and organolithium reagents. (a) General scheme for reactions of allylic substrates with organolithium compounds. (b) Reaction of allyl bromides with primary alkyl lithium reagents using Taniaphos. (c) Reaction of allyl bromides, chlorides or ethers with primary alkyl lithium reagents using (S,S,S)-L2. (d) Reaction of allyl chlorides with secondary alkyl lithium reagents using (S,R,R)-L3. (e) Reaction of trisubstituted (E)-allyl bromides with primary alkyl lithium reagents using (S,R,R)-L4. (f) Reaction of trisubstituted (Z)-allyl bromides with primary alkyl lithium reagents using (R,R,R)-L5. Red color: leaving groups; blue color: alkyl groups arising from the organolithium reagents: if $R^2 = \text{H}$, L1, L2 or L3 is used. If $R^2 = \text{CH}_3$, L4 or L5 is used.

The catalytic AAA reaction does not work for substrates bearing aldehyde, ketone or nitrile functional groups, all of which are known to undergo rapid 1,2-addition with organolithium reagents. Remarkably, high regioselectivity and a high enantiomeric ratio (e.r.) can be obtained with allyl bromides bearing an unprotected hydroxyl group, without the formation of any side products¹³.

Importantly, the method tolerates not only ferrocenyl-based ligands but also phosphoramidite ligands when applied to allyl chlorides. In particular, the coupling of secondary alkyl lithium reagents, which constituted a limitation when using Taniaphos-based catalysts, can be overcome with phosphoramidite ligands^{14,25} (Fig. 2b,c).

One of the major advantages of the AAA transformations is that it generates a terminal olefin next to the carbon stereogenic center. The terminal olefin is a highly versatile moiety for further functionalization; examples of transformations that we do in our lab include reductive ozonolysis, hydroboration oxidation,

intramolecular Heck reactions and ring-closing metathesis⁹. Using organolithium reagents as nucleophiles, we developed a one-pot synthesis of β - and γ -alkyl-substituted alcohols in which a tandem copper-catalyzed AAA reaction is followed by either reductive ozonolysis or by hydroboration and oxidation, respectively¹⁵.

Our group also developed a method for the preparation of all-carbon quaternary stereogenic centers with high regioselectivity and enantioselectivity, via copper-catalyzed AAA of trisubstituted allyl bromides with organolithium reagents (Fig. 2d)¹⁴. The control of the absolute stereochemistry in the formation of all-carbon quaternary stereogenic centers is considered a major synthetic challenge in organic synthesis²⁶, especially for acyclic systems, in which the number of degrees of freedom related to these acyclic substrates is high. As part of this method development, we studied the influence of the *E* or *Z* geometry of the prochiral trisubstituted allylic substrate on the stereochemical outcome of the copper-catalyzed AAA (Fig. 2e)¹⁶. In some cases,

Figure 3 | Examples of Cu-catalyzed AAA reactions. (Top) Reaction of cinnamyl bromide with $n\text{-BuLi}$. (Center) Reaction of **1b** with MeLi . (Bottom) Reaction using a highly sensitive ester-substituted allylic substrate **1c** with $n\text{-BuLi}$

the reaction of (*Z*)-allyl bromides affords higher selectivity than that obtained using (*E*)-allyl bromides, therefore providing an alternative for the synthesis of all-carbon quaternary centers.

We have also evaluated the use of alkyl- and benzyl-protected allyl ethers as substrates in Cu-catalyzed AAA with organolithium reagents¹⁷. These robust ether groups have a dual function; initially they act as protecting groups through a synthetic sequence, but when desired, the ether moiety can be activated to act as a leaving group for the AAA reaction. The use of a mixture of the Lewis acids $\text{BF}_3 \cdot \text{OEt}_2$ and trimethylsilyl trifluoromethanesulfonate (TMSOTf) (1:3)²⁷ in combination with highly reactive organolithium reagents was found to be essential for the activation of the less reactive acyclic allyl ethers in AAA (Fig. 2b). Finally, we have also developed a highly regio-, enantio- and anti-selective procedure for the catalytic asymmetric ring opening of oxabicyclic alkenes using organolithium reagents for the first time¹⁸. The use of $\text{BF}_3 \cdot \text{OEt}_2$ proved to be necessary for the activation of the oxabicyclic alkene.

Experimental design

This protocol consists of a general procedure for the enantioselective alkylation of allyl bromides, chlorides and ethers with alkyllithium compounds, using a Cu-based catalyst system. It includes a description of an appropriate reaction setup, ¹H-NMR, GC-MS and chiral HPLC methods to assess the regioselectivity and enantioselectivity of the reaction, and workup, purification and characterization of the product. Organolithium reagents are air- and moisture-sensitive, and therefore the reactions need to be performed under an inert atmosphere. For this protocol, dilution of the organolithium reagent with *n*-hexane (to reach a final concentration of 0.3 M) is required. The resulting solution is added over 2–10 h to a solution of the catalyst and allylic system in dichloromethane at –80 °C. An exception is the use of methyllithium, for which toluene should be used for dilution and addition, as the use of *n*-hexane as cosolvent results in problems with the addition because of poor solubility of MeLi in this solvent. Dilution with more polar solvents such as diethyl ether or tetrahydrofuran (THF) markedly lowers both regioselectivity and enantioselectivity, presumably because of their ability to disaggregate the organolithium reagent, which increases their reactivity. Allyl substrates, as well as Taniaphos and phosphoramidite ligands, are stable when handled in air. However, it is recommended that they be stored in a tightly capped vial at 5 °C, preferably under argon or nitrogen atmosphere. The copper salts are also air-stable, although they should be kept in a desiccator, preferably under Ar or N₂.

Reactions of allyl bromides with primary alkyllithium compounds require the use of 5 mol% of $\text{CuBr} \cdot \text{SMe}_2/(R,R)$ -Taniaphos

(**L1**) (obtained *in situ* by mixing the copper salt precursor $\text{CuBr} \cdot \text{SMe}_2$ (5 mol%) and the (*R,R*)-Taniaphos (**L1**) (6 mol%) in dry CH_2Cl_2) or $\text{CuBr} \cdot \text{SMe}_2/(S,S,S)$ -**L2** catalysts (similarly obtained by mixing the copper salt precursor $\text{CuBr} \cdot \text{SMe}_2$ (5 mol%) and phosphoramidite (*S,S,S*)-**L2** (5.5 mol%)). The use of allyl chlorides as substrates requires the use of 5 mol% of the $\text{CuBr} \cdot \text{SMe}_2/(S,S,S)$ -**L2** catalyst for primary alkyllithium compounds and the $\text{CuBr} \cdot \text{SMe}_2/(S,R,R)$ -**L3** catalyst for secondary alkyllithium compounds. For the synthesis of all-carbon quaternary stereogenic centers using *E*-trisubstituted allyl bromides, the $\text{CuBr} \cdot \text{SMe}_2/(S,R,R)$ -**L4** catalyst is used and the $\text{CuBr} \cdot \text{SMe}_2/(R,R,R)$ -**L5** catalyst is used in the case of *Z*-trisubstituted allyl bromides. All the aforementioned catalyst systems consist of a 1:1 Cu/ligand mixture. Finally, the more robust allyl ethers require the use of a $\text{BF}_3 \cdot \text{OEt}_2/\text{TMSOTf}$ mixture (which *in situ* generates the new Lewis acid BF_3OTf) for their activation in combination with the $\text{CuTC}/(S,S,S)$ -**L2** catalyst. In this case, a 1:2 Cu/ligand mixture is required to obtain optimal results. These reactions can be scaled up to produce gram quantities (tested with 5 mmol of **1a** as starting material) using a lower catalyst loading (2 mol%), in which the alkylated product is obtained with similar yield and e.r. (83% yield, S_N2'/S_N2 83:17, 99:1 e.r., Fig. 3, top).

The first example of this protocol describes the Cu-catalyzed AAA of cinnamyl bromide **1a** with *n*-BuLi, using the *in situ*-prepared $\text{CuBr} \cdot \text{SMe}_2/(R,R)$ -Taniaphos (**L1**) catalyst (Fig. 3 top).

The second example illustrates the introduction of a methyl group, among the most frequently encountered motifs in natural products, by reaction between methyllithium and benzyl protected (*E*)-4-bromobutenol **1b** using the $\text{CuBr} \cdot \text{SMe}_2/(R,R)$ -Taniaphos (**L1**) catalyst (Fig. 3, center). The third example shows the compatibility of a sensitive ester-substituted allylic substrate **1c**, bearing a heteroatom directly at the γ -position, in the alkylation reaction with *n*-BuLi using the $\text{CuBr} \cdot \text{SMe}_2/(R,R)$ -Taniaphos (**L1**) catalyst. The corresponding ester-protected allylic alcohol **2c** was obtained as the exclusive product in an 82% isolated yield and 99:1 e.r. (Fig. 3, bottom). In the fourth example, the use of the $\text{CuBr} \cdot \text{SMe}_2/(S,R,R)$ -**L3** catalyst system allows for the coupling of a secondary alkyllithium compound with an allyl chloride bearing a *p*-chloro-phenyl substituent **1d**. The reaction proceeds without lithium–halogen exchange despite the expected reactivity of organolithium compounds toward this transformation (Fig. 4, top).

In the fifth example, the use of $\text{CuBr} \cdot \text{SMe}_2/(S,R,R)$ -**L4** provides an all-carbon quaternary stereogenic center in an enantioselective manner (Fig. 4, bottom). The nature of the *ortho* substituents on the aryl ring plays an important role in the enantioselective outcome of the reaction; whereas simple methyl groups afford nearly racemic products, the corresponding bromo or methoxy substituents enhance the enantioselectivity. As before, no traces of halogen–lithium exchange were observed in these transformations.

The final example details the asymmetric alkylation of an allyl ether using *n*-HexLi in the presence of the $\text{CuTC}/(S,S,S)$ -**L2**

Figure 4 | Examples of Cu-catalyzed AAA reactions. (Top) Cu-catalyzed AAA involving a secondary alkyllithium compound with an allyl chloride. (Bottom) Enantioselective copper/phosphoramidite-catalyzed synthesis of quaternary carbon atoms using *n*-hexyllithium.

Figure 5 | Example of copper-catalyzed AAA of an allyl ether with organolithium reagents.

catalyst. Importantly, the use of $\text{BF}_3 \cdot \text{OEt}_2/\text{TMSOTf}$ is essential to the successful formation of this C–C bond. Access to the corresponding alkylated product allowed the shortest enantioselective synthesis of the biologically relevant (*S*)-arundic acid (**Fig. 5**)²⁸.

Limitations

The use of CH_2Cl_2 as a solvent and slow addition of the organolithium compound are always needed for successful implementation

of this protocol. Allylic systems bearing highly sensitive functional groups that would preferentially react with the aryllithium reagents (for instance, aldehydes, ketones, nitriles groups or imines) are unlikely to be suitable for this protocol. The use of aryllithium reagents provided predominantly linear products and poor regioselectivity when Taniaphos is used. Nonetheless, high enantioselectivity and moderate regioselectivity are possible with these reagents if phosphoramidite ligands are used instead.

MATERIALS

REAGENTS

▲ CRITICAL Anhydrous solvents, including *n*-hexane, THF, toluene and CH_2Cl_2 , should be freshly taken from an mBraun SPS-800 solvent purification dispenser equipped with anhydrous alumina columns.

- Ethyl acetate (ACS grade; Fisher Scientific, cat. no. UN1173)
- Dichloromethane (CH_2Cl_2 ; ACS grade; EMD Millipore, cat. no. MDX0835-3)
- Diethyl ether (ACS grade, stabilized; Fisher Scientific, cat. no. E138-4)
- Hexane, anhydrous (Sigma-Aldrich, cat. no. 296090)
- Tetrahydrofuran (THF), anhydrous (Sigma-Aldrich, cat. no. 401757-18L-P1)
- Toluene, anhydrous (Sigma-Aldrich, cat. no. 244511)
- Absolute ethanol or acetone for cooling bath
- Cinnamyl chloride, 95% purity (Sigma-Aldrich, cat. no. 187186)
- Cinnamyl bromide, 97% purity (Sigma-Aldrich, cat. no. C81217)
- Allyl halides **1b** (ref. 23), **1c** (ref. 29) **1d** (ref. 30), **1e** (ref. 25) and allyl ether **1f** (ref. 17), prepared in accordance with procedures from the literature
- Methylolithium (MeLi; 1.6 M in diethyl ether; Sigma-Aldrich, cat. no. 197343)
- Ethyllithium (EtLi; 0.5 M in benzene:cyclohexane; Sigma-Aldrich, cat. no. 561452)
- Hexyllithium (HexLi; 2.3 M in hexane; Sigma Aldrich, cat. no. 468568)
- sec*-butyllithium (*s*-BuLi; 1.4 M in cyclohexane; Sigma-Aldrich, cat. no. 195596)
- Isopropyllithium (*i*-PrLi; 0.7 M in *n*-pentane; Sigma-Aldrich, cat. no. 529745)
- n*-Butyllithium (*n*-BuLi; 1.6 M solution in hexane; Acros, cat. no. 181271000) **▲ CRITICAL** Organolithium compounds are highly reactive species. They are corrosive, flammable and sometimes pyrophoric, and they can also undergo thermal decomposition. Organolithium reagents should be stored below 10 °C.
- Copper(I) bromide dimethyl sulfide complex ($\text{CuBr} \cdot \text{SMe}_2$; 99%; Sigma-Aldrich, cat. no. 230502) $\text{CuBr} \cdot \text{SMe}_2$ should be stored in a desiccator, preferably under N_2 or Ar
- Copper(I) thiophene-2-carboxylate (CuTC; Sigma-Aldrich, cat. no. 682500). CuTC should be stored in a desiccator, preferably under N_2 or Ar
- (*R_p*)-1-[(*R*)- α -(dimethylamino)-2-(diphenylphosphino)benzyl]-2-diphenylphosphinoferrocene, (*R,R*)-Taniaphos (**L1**), optical purity (enantiomeric excess (ee)): $\geq 99\%$ (Sigma-Aldrich, cat. no. 73475)
- Phosphoramidite ligands **L2** (ref. 31), **L3**, **L5** (ref. 32) and **L4** (refs. 33,34), prepared as reported in literature
- Boron trifluoride diethyl etherate ($\text{BF}_3 \cdot \text{OEt}_2$; Sigma-Aldrich, cat. no. 175501) **! CAUTION** This chemical reacts violently with water. It should be handled under inert atmosphere.
- Trimethylsilyl trifluoromethanesulfonate (TMSOTf; 99%; Sigma-Aldrich, cat. no. 225649) **! CAUTION** This chemical reacts violently with water. It should be handled under inert atmosphere.
- Anhydrous sodium sulfate (Na_2SO_4 ; Sigma-Aldrich, cat. no. 239313)
- SiO_2
- Basic alumina
- Celite 535 (Sigma-Aldrich, cat. no. 22138)

EQUIPMENT

- Weighing balance (Kern)
- Analytical semi-micro balance (Mettler, model no. Toledo AX205, delta range)
- Vials with Teflon-lined caps (Brown, cat. no. 150745)
- Teflon-coated magnetic stir bar (VWR, cat. no. 442-0295)

- Magnetic stir plate (IKA, RCT basic)
- Higher-pressure programmable single syringe pump (New Era, model no. 1000)
- Spatula
- GC vials and screw caps (Brown, cat. nos. 151123 and 151216)
- Dry solvent dispenser (MBRAUN, model no. MB-SPS-800)
- Nitrogen-vacuum manifold equipped with a Tygon tubing and an oil-filled bubbler
- Immersion cooler (cryostat) with immersion probe for rapid cooling of liquids (working temperature down to -90°C) (Julabo, model no. FT902)
- Cryogenic storage Dewar for the cooling bath
- TLC plate, cuvette and spotter
- Schlenk-type vessels (25–100 ml)
- Rubber septa (Suba Seal)
- Round-bottom flasks (50–500 ml)
- Erlenmeyer flask (25–100 ml)
- Silica gel for column chromatography
- Rotary evaporator (IKA, RV 8)
- Separatory funnel (50–100 ml)
- Pasteur pipettes
- Rubber bulb for Pasteur pipettes
- Column for flash chromatography (1 cm $\times$ 20–40 cm)
- Tubes for collecting column chromatography fractions
- Syringes (1–10 ml) and needles
- Access to NMR, mass spectrometry, chiral-GC and chiral-HPLC (Equipment Setup)
- Parafilm M (Sigma-Aldrich, cat. no. BR701605)

REAGENT SETUP

Copper salt precursors, ligands and allylic substrates $\text{CuBr} \cdot \text{SMe}_2$, CuTC, (*R,R*)-Taniaphos, phosphoramidite ligands and allylic substrates can be weighed in air. If $^1\text{H}/^{31}\text{P}$ -NMR reveals the presence of impurities in the allylic substrates or phosphoramidite ligands, they should be repurified by column chromatography or resynthesized in accordance with procedures from the literature (REAGENTS).

Organolithium compounds Aryllithium compounds should be newly purchased. Otherwise, they should be titrated by standard procedures before use (i.e., by using diphenylacetic acid³⁵ or salicylaldehyde phenylhydrazones³⁶). To keep the solutions of organolithium reagents free from air and moisture, a Tygon tube attached to the nitrogen supply and fitted with a needle should be inserted through the white SureSeal top of the bottle to maintain its contents under a positive pressure of nitrogen. The organolithium solution should then be collected through the SureSeal septum using a syringe fitted with a second needle. After use, the SureSeal should be covered with Parafilm and the bottle should be closed and wrapped with Parafilm.

▲ CRITICAL Partially quenched organolithium solutions may lower the conversion, regioselectivity and enantioselectivity of the alkylation reaction.

Solvents Dry CH_2Cl_2 , toluene and *n*-hexane (collected from the dry solvent dispenser) can be stored under N_2 in a 100- to 500-ml Schlenk vessel capped with a Teflon-lined cap. The amount of water (p.p.m.) in these solvents should be minimal and can be determined by Karl Fischer titration³⁷ before use. To allow the solvent to be taken for the alkylation reactions, the Schlenk vessel must be attached to the N_2 supply through a hose to maintain its content under a positive pressure of N_2 . The solvent is then collected through the Teflon-lined cap using a syringe and transferred to the Schlenk vessel.

EQUIPMENT SETUP

Reaction flask Schlenk tubes for the reactions should be dried in an oven for at least 30 min at 140 °C or preheated using a heat gun.

Analytical facilities In our laboratory GC–MS analyses were performed on a Shimadzu high-end GC–MS using a 30 m × 0.25 mm capillary column (+0.25 µm film thickness) with polysiloxane as the stationary phase. A typical method used for this copper-catalyzed AAA is as follows: (i) 40 °C oven temperature upon injection, (ii) increase the temperature to 250 °C over 21 min and (iii) hold it at 250 °C for 5 min. Chiral GC analyses were performed on a

Hewlett Packard (HP 6890 Series) or Agilent (7890A GC System) apparatus equipped with an FID detector using 30 m × 0.25 mm × 0.25 µm columns containing chiral stationary phases. An example of the column used is CHIRALDEX (incorporate phases consisting of derivatives of α -, β - or γ -cyclodextrin bonded to dimethylpolysiloxane). Chiral HPLC analyses were performed on a Shimadzu apparatus equipped with a diode array detector (SPD-M20A) using 3.6 mm × 250 mm columns containing chiral stationary phases (5-µm particle size). Examples of chiral columns used are CHIRALCEL OD-H, CHIRALCEL OJ-H, CHIRALPAK AD-H and CHIRALPAK AS-H.

PROCEDURE

In situ preparation of the copper-chiral ligand-based catalytic system ● TIMING 35 min

1| Weigh out CuBr·SMe₂ (5 mol%) (for the AAA of allyl halides with alkylolithium reagents) or CuTC (5 mol%) (for the AAA of allyl ethers with alkylolithium reagents). The amounts used for the compounds listed in the ANTICIPATED RESULTS section are summarized below.

	CuBr·SMe ₂	CuTC
(+)-(S)-hept-1-en-3-ylbenzene (2a) ^a	2.1 mg, 0.01 mmol	–
(+)-(S)-hept-1-en-3-ylbenzene (2a) ^b	21 mg, 0.1 mmol	–
(-)-(S)-(((2-methylbut-3-en-1-yl)oxy)methyl)benzene (2b) ^a	2.1 mg, 0.01 mmol	–
(+)-(S)-hept-1-en-3-yl benzoate (2c) ^a	2.1 mg, 0.01 mmol	–
(+)-(S)-1-chloro-4-(4-methylpent-1-en-3-yl)benzene (2d) ^a	2.1 mg, 0.01 mmol	–
(+)-1-bromo-2-(3-methylnon-1-en-3-yl)benzene (2e) ^a	2.1 mg, 0.01 mmol	–
(S)-4-vinyldecane (2f) ^a	–	1.9 mg, 0.01 mmol

^aReaction performed on a 0.2-mmol scale using 5 mol% of catalyst.

^bReaction performed on a 5.0-mmol scale using 2 mol% of catalyst.

? TROUBLESHOOTING

2| Add (*R,R*)-Taniaphos (**L1**) (6 mol%) or the corresponding phosphoramidite ligand (5.5–10 mol%) (ANTICIPATED RESULTS) to an Eppendorf tube or a vial.

	(<i>R,R</i>)-Taniaphos (L1)	Phosphoramidite ligand
2a	8.3 mg, 0.012 mmol ^a	–
2a	83 mg, 0.12 mmol ^b	–
2b	8.3 mg, 0.012 mmol ^a	–
2c	8.3 mg, 0.012 mmol ^a	–
2d	–	(<i>S,R,R</i>)- L3 , 5.9 mg, 0.011 mmol, 5.5 mol% ^a
2e	–	(<i>S,R,R</i>)- L4 , 5.9 mg, 0.011 mmol, 5.5 mol% ^a
2f	–	(<i>S,S,S</i>)- L2 , 13 mg, 0.022 mmol, 11 mol% ^a

^aReaction performed on a 0.2-mmol scale using 5 mol% of catalyst.

^bReaction performed on a 5.0-mmol scale using 2 mol% of catalyst.

3| Add the contents to an oven-dried Schlenk-type vessel, which has been allowed to cool to room temperature (22 °C) under vacuum and backfilled with Ar or N₂ before use.

4| Cap the vessel with a rubber septum, evacuate it and backfill it with Ar or N₂. Repeat the evacuation and backfilling procedure one more time.

5| Add CH₂Cl₂ (10 ml per mmol of substrate) via a syringe, and stir the mixture for ~15 min at room temperature.

Figure 6 | Taking a solution of allyl halide with a syringe to transfer to the reaction vessel.

Figure 7 | Reaction vessel immersed in the cooling bath at $-80\text{ }^{\circ}\text{C}$.

- 6** | Weigh out the allyl halide or ether (1.0 equiv.) in a vial and cap the vial with a Teflon-lined cap. The amounts used for the compounds listed in the ANTICIPATED RESULTS section are summarized below.

Cinnamyl bromide (1a)	0.2 mmol, 39 mg
Cinnamyl bromide (1a) ^a	5.0 mmol, 986 mg
(<i>E</i>)-(((4-bromobut-2-en-1-yl)oxy)methyl)benzene ²² (1b)	0.2 mmol, 48 mg
(<i>E</i>)-3-bromoprop-1-en-1-yl benzoate (1c)	0.2 mmol, 48 mg
(<i>E</i>)-1-chloro-4-(3-chloroprop-1-en-1-yl)benzene ²⁹ (1d)	0.2 mmol, 37 mg
(<i>E</i>)-1-bromo-2-(4-bromobut-2-en-2-yl)benzene (1e) ²⁴	0.2 mmol, 58 mg
(<i>E</i>)-((hex-2-en-1-yloxy)methyl)benzene (1f) ¹⁶	0.2 mmol, 38 mg

^aReaction performed on a 5-mmol scale using a lower catalyst loading (2 mol%).

? TROUBLESHOOTING

- 7** | Connect a needle to the Ar or N₂ manifold, and insert the needle through the Teflon cap.
- 8** | Evacuate the vial and fill it again with Ar or N₂. Add CH₂Cl₂ (5 ml per mmol of substrate) using a syringe, and transfer the resulting solution with the same syringe to the reaction mixture (**Fig. 6**).
- ▲ CRITICAL STEP** During the addition of the solution of allylic substrate, the needle should be straight and located into the center of the vessel, and the drops should fall directly into the reaction mixture.
- Injecting the solution along the walls of the Schlenk vessel may result in lower conversion of starting materials.
- 9** | Immerse the Schlenk flask containing the reaction mixture in the cooling bath at $-80\text{ }^{\circ}\text{C}$, the temperature of which should be monitored by a thermocouple, and stir vigorously (**Fig. 7**). The vessel should be under a positive pressure of Ar or N₂.
- ▲ CRITICAL STEP** The temperature of the reaction vessel should never exceed $-60\text{ }^{\circ}\text{C}$, as at higher temperatures alkylolithium compounds might react with CH₂Cl₂ to form carbenes³⁸.

Preparation of the solution containing a mixture of Lewis acids ● TIMING 30 min

▲ CRITICAL Steps 10–16 are only for Cu-catalyzed AAA reactions using allyl ethers as substrates (for example, compound **1f**). If you are performing reactions with allyl halides (for example, compounds **1a–e**) continue to Step 17.

- 10** | Prepare a second oven-dried-Schlenk-type vessel equipped with a Teflon-coated magnetic stir bar and a rubber septum.

11| Evacuate the vessel while hot, and fill it with Ar or N₂. After cooling it to room temperature, add CH₂Cl₂ (2.5 ml per mmol of substrate), immerse the vessel in the cooling bath at –80 °C, and stir vigorously.

▲ **CRITICAL STEP** The Schlenk tube should be under a positive pressure of Ar or N₂.

12| Secure the bottles of BF₃·OEt₂ and TMSOTf by clamping them to the rack in the fume hood.

13| Connect two needles to the Ar or N₂ manifold, and insert the needles through the Teflon-lined cap of the bottles.

14| Transfer TMSOTf (1.1 ml per mmol of substrate, 6.0 equiv.) by syringe to the vessel.

15| Transfer BF₃·OEt₂ (250 µl per mmol of substrate, 2.0 equiv.) to the resulting solution using a syringe, and stir the mixture for ~15 min.

16| Add the corresponding volume of the resulting 'BF₂·OTf' solution to the reaction vessel (3.0 ml per mmol of substrate, 2.0 equiv.) using a syringe.

▲ **CRITICAL STEP** BF₃·OEt₂ and TMSOTf compounds are air- and moisture-sensitive. The presence of oxygen or humidity in a reaction vessel, as well as the use of aged or partially hydrolyzed solutions of these reagents, will result in a lower or no conversion of starting materials, diminished regioselectivity and enantioselectivities, and reduced yields of products.

Preparation of the solution of the organolithium compounds ● **TIMING 10 min**

17| Equip another oven-dried-Schlenk-type vessel with a Teflon-coated magnetic stir bar and a rubber septum.

18| Evacuate the vessel while hot, and backfill it with Ar or N₂, and let it cool to room temperature.

19| Add the corresponding amount of *n*-hexane (for alkyllithium compounds other than methyllithium) or toluene (for methyllithium) to obtain a final concentration of 0.23–0.3 M. The alkyllithium reagents used for the synthesis of the compounds listed in the ANTICIPATED RESULTS section are summarized below. Brand-new bottles of organolithium reagents should be used for the preparation of these compounds.

Alkyllithium compound^a and cosolvent used for the dilution

2a	<i>n</i> -BuLi (1.2 equiv., 750 µl per mmol of 1a , 1.6 M) diluted with hexane (4.3 ml per mmol of 1a)
2b	MeLi (1.2 equiv., 750 µl per mmol of 1b , 1.6 M) diluted with toluene (4.3 ml per mmol of 1b)
2c	<i>n</i> -BuLi (1.1 equiv., 650 µl per mmol of 1c , 1.6 M) diluted with hexane (4.5 ml per mmol of 1c)
2d	<i>i</i> -PrLi (1.2 equiv., 1.75 ml per mmol of 1d , 0.7 M) diluted with hexane (3.3 ml per mmol of 1d)
2e	<i>n</i> -HexLi (1.2 equiv., 525 µl per mmol of 1e , 2.3 M) diluted with hexane (4.5 ml per mmol of 1e)
2f	<i>n</i> -HexLi (1.5 equiv., 650 µl per mmol of 1f , 2.3 M) diluted with hexane (4.4 ml per mmol of 1f)

^aThe corresponding amounts refer to fresh bottles of organolithium reagents.

20| Using a clamp, secure the bottle of organolithium to the rack in the back of the fume hood.

21| Connect a needle to the Ar or N₂ manifold, and insert the needle through the Teflon-lined cap of the bottle of organolithium compound (**Fig. 8**).

22| Using a syringe, transfer the corresponding volume of the organolithium solution to the Schlenk flask (**Fig. 9**). The vessel should be under a positive pressure of Ar or N₂. Stir the solution for ~30 s.

▲ **CRITICAL STEP** Organolithium compounds are air- and moisture-sensitive. The presence of oxygen or humidity in the reaction vessel will result in a lower or no conversion of starting materials, diminished regioselectivity and enantioselectivities, and reduced yields of products. For actual volumes of organolithium compounds for selected reactions, see ANTICIPATED RESULTS.

Figure 8 | Taking a solution of commercial organolithium compound with a syringe under a N_2 atmosphere.

Figure 9 | Preparing a solution of the organolithium compound.

Addition of the organolithium compound to the reaction mixture ● TIMING 2–10 h

23 | Transfer the solution of the organolithium compound slowly to the reaction mixture by syringe over 2–10 h using a syringe pump (**Fig. 10**). The addition times for the organolithium reagents for the synthesis of the compounds listed in the ANTICIPATED RESULTS section are summarized below.

	Organolithium reagent	Addition time (h)
2a	<i>n</i> -BuLi	2
2b	MeLi	2
2c	<i>n</i> -BuLi	2
2d	<i>i</i> -PrLi	5
2e	<i>n</i> -HexLi	10
2f	<i>n</i> -HexLi	2

▲ **CRITICAL STEP** The needle should be straight and located at the center of the vessel, and the drops of organolithium solution should fall directly into the reaction mixture. Injecting the organolithium solution along the walls of the Schlenk vessel may result in lower conversion of starting materials. (For the actual addition time, see ANTICIPATED RESULTS.)

▲ **CRITICAL STEP** To avoid high local concentration of organolithium solution, stir the reaction mixture rapidly. However, ensure that the stirring is not so vigorous that it causes deposition of the aryl halide solution over the sides of the flask above the solvent line. In this scenario, full conversion may not be achieved.

? TROUBLESHOOTING

■ **PAUSE POINT** Cu-catalyzed AAA reactions with organolithium compounds take more than 2 h. For the use of (*R,R*)-Taniaphos (**L1**), >5 h is needed for the transformations using phosphoramidite ligands and >10 h is needed for the synthesis of all-carbon quaternary stereogenic centers using (*E*)-trisubstituted allyl bromides and $CuBr \cdot SMe_2/(S,R,R)$ -**L4**.

Reaction workup and purification ● TIMING 1–3 h

24 | After the addition is complete, add a saturated aqueous solution of NH_4Cl (1–10 ml per mmol of substrate) through the septum by syringe, and stir the mixture for ~1 min at $-80^\circ C$.

25 | Remove the vessel from the cooling bath and allow the reaction mixture to warm to room temperature. Next, stir the mixture for ~5 min at room temperature.

26 | Transfer the mixture to a separation funnel and wash the reaction vessel with CH_2Cl_2 (2×1 –5 ml per mmol of substrate).

27 | Separate the organic phase by transferring the mixture to a 50-ml Erlenmeyer flask.

28| Extract the aqueous phase three times with CH_2Cl_2 (5–25 ml per mmol of substrate) and combine all the organic phases in the same Erlenmeyer flask.

29| Dry the solution over anhydrous solid sodium sulfate. For this purpose, allow the solution to stand over sodium sulfate for 10 min, and filter or carefully decant the liquid, leaving behind sodium sulfate.

30| Concentrate the solution under reduced pressure using a rotary evaporator at a temperature of 25–40 °C.
■ PAUSE POINT Products that are air and thermally stable can be stored in crude purity overnight in a sealed flask in a refrigerator at 5 °C.

31| Purify the crude product by flash chromatography³⁹ on silica gel using mixtures of *n*-pentane and ethyl acetate or Et_2O , in which the product spot on a TLC plate displays an R_f of 0.30–0.40.

32| Collect the fractions that contain the product into a round-bottom flask, and remove the solvent using a rotary evaporator at a temperature of 25–30 °C. Remove trace amounts of solvent using the vacuum manifold.

■ PAUSE POINT Substrates that are nonvolatile can be left overnight under vacuum.

33| Analyze the structure and purity of the resulting AAA product by NMR and the techniques described in the EQUIPMENT section.

Figure 10 | Adding the organolithium solution using a syringe pump.

Figure 11 | HPLC traces of phenacyl ester of (*S*)-Arundic acid 4. (a) The trace for the racemic ester. (b) The trace for the enantiopure ester. mAu, milliabsorbance units; Pk, peak.

Determination of regioselectivity and enantiomeric ratio ● TIMING 1 h

34| To determine the regioselectivity, record an ^1H -NMR spectrum of the material obtained in Step 30 and compare the integral value between similar signals in the $\text{S}_{\text{N}}2'$ and $\text{S}_{\text{N}}2$ products.

? TROUBLESHOOTING

35| Determine the e.r. by injecting an aliquot of the material obtained in Step 32 into the HPLC or GC column equipped with a chiral column after calibrating the retention time of the enantiomers with the authentic racemic sample; see ANTICIPATED RESULTS.

? TROUBLESHOOTING

? TROUBLESHOOTING

Troubleshooting advice can be found in **Table 1**.

TABLE 1 | Troubleshooting table.

Step	Problem	Possible reason	Solution
1,6	Solids stick to the vial and around the neck of the reaction vessel	Static electricity due to dry reagents, vial and glass	Use an antistatic gun to remove static electricity from the neck of the tube and vial Weigh the solids in an Eppendorf tube instead of a vial
23	Organolithium compound is deposited on the tip of the needle	The N_2 or Ar flow from the manifold evaporates the drops of organolithium solution	Close the Schlenk tap to the manifold during the addition
34, 35	Low conversion and yield and/or regioselectivity and enantioselectivity	(i) Allylic substrates or chiral ligands are degraded or not pure (ii) Organolithium reagents are partially quenched (iii) For Cu-catalyzed AAA using allylic ethers: $\text{BF}_3 \cdot \text{OEt}_2$ and TMSOTf are partially hydrolyzed (iv) Solvents are not pure (v) Copper complex is not formed (vi) Wrong ratio of reagents and catalyst (caused by loss during weighing and transfer procedures)	(i) Check NMR spectra of all starting materials for reagent purity. Repurify or acquire new materials as necessary (ii) Determine the real concentration of the organolithium reagent solutions by standard titration techniques or acquire new solutions (iii) Acquire new solutions (iv) Purify the solvents to remove reactive impurities such as water, other protic and/or acidic materials, or atmospheric contaminants such as oxygen (v) Stir the mixture of copper salt and ligand for at least 15 min at room temperature (vi) Repeat the procedure with special attention to point i

● TIMING

Steps 1–9, *in situ* preparation of the copper-chiral ligand-based catalytic system: 35 min

Steps 10–16, preparation of the solution containing a mixture of Lewis acids: 30 min

Steps 17–22, preparation of the solution of the organolithium compounds: 10 min

Step 23, addition of the organolithium compound to the reaction mixture: 2–10 h

Steps 24–33, reaction workup and purification: 1–2 h

Steps 34 and 35, determination of regioselectivity and enantiomeric ratio: 1 h

ANTICIPATED RESULTS

Preparation of (+)-(S)-hept-1-en-3-ylbenzene (2a):

See reaction scheme in **Figure 3**, top. Flash column chromatography on silica gel (2:98 Et_2O :*n*-pentane, $R_f = 0.8$) provided the title compound as a colorless oil. 0.2 mmol scale: (88% yield, >99:1 e.r.) obtained as a 90:10 mixture of $\text{S}_{\text{N}}2'/\text{S}_{\text{N}}2$ products. 5 mmol scale: (83% yield, 99:1 e.r.) obtained as an 83:17 mixture of $\text{S}_{\text{N}}2'/\text{S}_{\text{N}}2$ products. The physical data were identical in all respects to those previously reported⁴⁰. $[\alpha]_{\text{D}}^{20} = +49.4$ ($c = 1.0$, CHCl_3) (ref. 40). (97:3 e.r.): $[\alpha]_{\text{D}}^{20} = +47$ ($c = 0.5$, CHCl_3). ^1H -NMR (400 MHz, CDCl_3) δ 7.21 (m, 5H), 5.95 (m, 1H), 5.02 (m, 2H), 3.32 (q, $J = 7.5$ Hz, 1H),

1.70 (q, $J = 7.4$ Hz, 2H), 1.39–1.02 (m, 4H), 0.87 (t, $J = 7.0$ Hz, 3H) p.p.m. ^{13}C -NMR δ 144.7, 142.5, 128.4, 127.6, 126.0, 113.8, 49.9, 35.1, 29.7, 22.6, 14.0 p.p.m. Enantiomeric ratio was determined by chiral GC analysis, CP-Chirasil-Dex-CB (25 m $\times$ 0.25 mm), initial temp. 80 °C for 80 min, then 1 °C/min to 140 °C (hold for 5 min), then 10 °C/min to 180 °C (final temp.), retention times (min): 75.5 (minor) and 76.6 (major); retention time for S_N2 product: 127.5 min. Compound **2a** is stable over months when stored at 5 °C.

Preparation of (-)-(S)-(((2-methylbut-3-en-1-yl)oxy)methyl)benzene (2b)

See reaction scheme in **Figure 3**, center. Flash column chromatography on silica gel (1:99 Et₂O:*n*-pentane, $R_f = 0.5$) provided the title compound as a colorless oil (98% yield, 95:5 e.r.) obtained as an 85:15 mixture of S_N2'/S_N2 products. The physical data were identical in all respects to those previously reported⁴⁰. $[\alpha]_D^{20} = -3.6$ ($c = 1.0$, CHCl₃), (lit⁴⁰. (96:4 e.r.): $[\alpha]_D^{20} = -6$ ($c = 1.1$, CHCl₃)). ^1H -NMR (400 MHz, CDCl₃) δ 7.32 (d, $J = 4.5$ Hz, 4H), 7.29–7.21 (m, 1H), 5.83–5.74 (m, 1H), 5.07–4.99 (m, 2H), 4.50 (s, 2H), 3.36 (dd, $J = 9.1$ and 6.5 Hz, 1H), 3.28 (dd, $J = 9.1$ and 6.8 Hz, 1H), 2.52–2.44 (m, 1H), 1.03 (d, $J = 6.8$ Hz, 3H) p.p.m. ^{13}C -NMR δ 141.3, 138.6, 128.3, 127.5, 127.4, 114.0, 75.0, 72.9, 37.8, 16.6 p.p.m. MS (electron ionization (EI) mode) m/z (%): 176 (M^+ , 12), 175 (5), 92 (11), 91 (100), 65 (7). HRMS calcd. for C₁₂H₁₆O 176.12011; found 176.12262. e.r. was determined by chiral HPLC analysis, Chiralcel OD-H (99.75:0.25 (vol/vol) *n*-heptane:*i*-PrOH), 40 °C, retention times (min): 10.9 (minor) and 11.2 (major). Compound **2a** is stable over months when stored at 5 °C.

Preparation of (+)-(S)-hept-1-en-3-yl benzoate (2c)

See reaction scheme in **Figure 3**, bottom. Flash chromatography on silica gel (*n*-pentane:Et₂O 80:1, $R_f = 0.5$) provided 36 mg (82% yield, 99:1 e.r.) of (S)-hept-1-en-3-yl benzoate as a colorless oil. ^1H -NMR (400 MHz, CDCl₃) δ 8.08–8.06 (m, 2H), 7.56 (tt, $J = 7.4$, 1.4 Hz, 1H), 7.47–7.42 (m, 2H), 5.90 (ddd, $J = 17.0$, 10.5, 6.3 Hz, 1H), 5.52–5.47 (m, 1H), 5.32 (dt, $J = 17.3$, 1.3 Hz, 1H), 5.20 (dt, $J = 10.5$, 1.2 Hz, 1H), 1.85–1.68 (m, 2H), 1.45–1.30 (m, 4H), 0.91 (t, $J = 7.1$ Hz, 3H). ^{13}C -NMR (100 MHz, CDCl₃) δ 165.9, 136.6, 132.8, 130.6, 129.6, 128.3, 116.5, 75.3, 34.0, 27.2, 22.5, 14.0. HRMS (ESI+, m/z): calcd. for C₁₄H₁₈O₂Na $[M+Na]^+$: 241.11990; found: 241.12010. Enantiomeric ratio was determined by chiral HPLC analysis, on a Chiralcel OB-H column with *n*-heptane:*i*-PrOH 99.8:0.2 (vol/vol), flow = 0.5 ml/min, 40 °C, 225 nm. Retention times: 12.9 min [(S)-enantiomer (major)] and 15.1 min [(R)-enantiomer (minor)]. $[\alpha]_D^{20} = +31.2$ ($c = 1.0$, CHCl₃). Compound **2a** is stable over months when stored at 5 °C.

Preparation of (+)-(S)-1-chloro-4-(4-methylpent-1-en-3-yl)benzene (2d)

See reaction scheme in **Figure 4**, top. Flash column chromatography on silica gel (*n*-pentane, $R_f = 0.8$) provided the title compound as a colorless oil (95% yield, 96:4 e.r.) obtained as a 92:8 mixture of S_N2'/S_N2 . The physical data were identical in all respects to those previously reported⁴¹. $[\alpha]_D^{20} = +87.8$ ($c = 1.0$, CHCl₃). (lit⁴¹. (90:10 e.r.): $[\alpha]_D^{20} = +78.4$ ($c = 1.1$, CHCl₃)). ^1H -NMR (400 MHz, CDCl₃) δ 7.28–7.26 (m, 2H), 7.12–7.10 (m, 2H), 5.96 (m, 1H), 5.07–5.01 (m, 2H), 2.88 (t, $J = 8.8$ Hz, 1H), 1.92 (m, 1H), 0.96 (d, $J = 6.8$ Hz, 3H), 0.78 (d, $J = 6.8$ Hz, 3H) p.p.m. ^{13}C -NMR (100 MHz, CDCl₃): 142.8, 140.7, 131.6, 129.2, 128.6, 115.4, 57.8, 32.6, 20.9, 20.7 p.p.m. MS (EI mode) m/z (%): 194 (M^+ , 12), 151 (100), 115 (68). Enantiomeric ratio was determined by chiral GC analysis, CP-Chirasil-Dex-CB (25 m $\times$ 0.25 mm), initial temp. 85 °C for 60 min, then 5 °C/min to 175 °C (hold for 2 min), then 10 °C/min to 80 °C (final temp.), retention times (min): 73.1 (minor) and 73.6 (major); retention time S_N2 78.0 min. Compound **2a** is stable over months when stored at 5 °C.

Preparation of (+)-1-bromo-2-(3-methylnon-1-en-3-yl)benzene (2e)

See reaction scheme in **Figure 4**, bottom. Flash column chromatography on silica gel (*n*-pentane, $R_f = 0.8$) provided the title compound as a colorless oil (93% yield, 91:9 e.r.) obtained as a >98:2 mixture of S_N2'/S_N2 products. ^1H -NMR (400 MHz, CDCl₃) δ 7.57 (dd, $J = 7.9$, 1.3 Hz, 1H), 7.39 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.25 (td, $J = 7.7$, 1.3 Hz, 1H), 7.05 (td, $J = 7.7$, 1.6 Hz, 1H), 6.21 (dd, $J = 17.6$, 10.7 Hz, 1H), 5.09 (dd, $J = 10.7$, 1.0 Hz, 1H), 4.93 (dd, $J = 17.6$, 1.0 Hz, 1H), 2.29 (ddd, $J = 13.4$, 12.1, 4.7 Hz, 1H), 1.83 (ddd, $J = 13.4$, 12.4, 4.3 Hz, 1H), 1.51 (s, 4H), 1.30–1.09 (m, 7H), 1.01–0.88 (m, 1H), 0.86 (t, $J = 6.8$ Hz, 3H) p.p.m. ^{13}C -NMR (100 MHz, CDCl₃) δ 146.6, 145.2, 135.5, 129.6, 127.6, 126.9, 123.3, 112.2, 46.0, 38.7, 31.7, 29.9, 26.2, 24.5, 22.6, 14.1 p.p.m. $[\alpha]_D^{20} = +7.0$ ($c = 1.0$, CHCl₃). The e.r. was determined for the primary alcohol, obtained following the hydroboration and oxidation protocol of the terminal double bond²⁵. e.r. was determined by chiral HPLC analysis, Chiralcel AS-H column, *n*-heptane:*i*-PrOH 98:2 (vol/vol), 40 °C, 215 nm, retention times (min): 15.2 (minor) and 20.2 (major). MS (EI) m/z 296 (M^+ , 2), 294 (M^+ , 2), 212 (17), 210 (17), 198 (13), 196 (14), 171 (5), 169 (5), 145 (13), 130 (100), 115 (24), 91 (5). In accordance with the results obtained in the other allylic alkylations²⁵, the absolute configuration of this compound is proposed to be (R). Compound **2a** is stable over months when stored at 5 °C.

Preparation of (S)-4-vinyldecane (2f)

See reaction scheme in **Figure 5**. A 95:5 mixture of S_N2'/S_N2 (conversion of 100%, >99:1 e.r.) was obtained. The high volatility of the product **2f** did not allow for complete removal of the solvents after workup, impeding the determination of an accurate isolated yield. Alkene **2f** in CH_2Cl_2 , as obtained directly from the workup of the allylic alkylation, was treated by reductive ozonolysis. The corresponding alcohol was obtained in a 72% yield (overall yield for the two steps) and with a >99:1 e.r. The resulting alcohol was further oxidized using iodobenzene diacetate and TEMPO to afford Arundic acid **3** with a >99:1 e.r. and 94% yield (ref. 17; **Fig. 11**). The e.r. was determined by conversion of (S)-Arundic acid **3** to the corresponding phenacyl ester **4** (ref. 17). e.r. was determined by chiral HPLC analysis, Chiralcel OJ-H column, 0.5 ml/min, *n*-heptane:*i*-PrOH 99:1 (vol/vol), 40 °C, retention times (min): 17.7 (major) and 19.8 (minor).

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