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Counterion-Enhanced Pd/Enamine Catalysis: Direct Asymmetric α-Allylation of Aldehydes with Allylic Alcohols by Chiral Amines and Achiral or Racemic Phosphoric Acids

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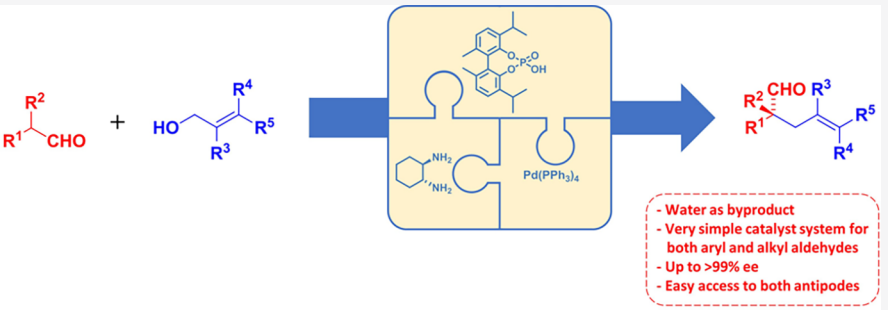

ABSTRACT: We report a straightforward and efficient Pd/enamine catalytic procedure for the direct asymmetric α-allylation of branched aldehydes. The use of simple chiral amines and easily prepared achiral or racemic phosphoric acids, together with a suitable Pd-source resulted in a highly active and enantioselective catalyst system for the allylation of various α-branched aldehydes with different allylic alcohols. The reported procedure could provide an easy access to both product antipodes. Furthermore, two possible orthogonal derivatizations of the enantioenriched aldehydes were performed without any decrease in enantioselectivity.

INTRODUCTION

Carbon−carbon bond-forming reactions were always in the focus of organic chemistry. The synthesis of asymmetric all-carbon quaternary centers is particularly challenging, and despite the growing numbers of advances in this field, it is still a difficult task because of the substantial steric repulsion between the reactants.[1,2]

Optically active molecules bearing an allylic motif are invaluable intermediates for the total synthesis of biologically active compounds.[3,4] Based on the pioneering work of Jirō Tsuji and Barry M. Trost, the palladium-catalyzed asymmetric allylation involving an in situ-generated allylpalladium−π complex is of special interest in this field. Thanks to the indisputable advantages such as mild reaction conditions and operational simplicity, it is still a crucial tool for the synthesis of allylic compounds.[5]

While the traditional Tsuji−Trost allylation requires both a good nucleophile and an allylic compound with a suitable leaving group, several advances have been published to overcome this problem by merging organo− and transition−-metal catalyses. In 2003, Krische and coworkers achieved enone cycloallylations via dual activation of latent nucleophilic and electrophilic partners.[6] Three years later, Córdova reported the first Pd/enamine dual catalyst system relying on $Pd(PPh_3)_4$ and pyrrolidine in the direct α-allylation of nonbranched aldehydes and ketones with activated allylic electrophiles.[7] Since then, enamine catalysis has played an important role in the field of asymmetric allylation.[8−11] A few elegant procedures have also been found for the asymmetric α-allylation of branched aldehydes including the synergistic use of a Pd-source with modified primary amino acids (Yoshida, Scheme 1a) or iridium catalysis with double stereocontrol (Carreira).[12−16] By expanding the use of their previously established concept of asymmetric counteranion-directed catalysis to asymmetric allylations, the List group developed a three-component-catalyst system composed of a Pd-complex, an amine, and a chiral Brønsted acid known as TRIP (Scheme 1b).[17−20] Even though the synthesis of TRIP requires a multistep procedure and results in a rather pricy catalyst, they achieved impressive catalytic activities together with a high degree of enantioselectivity (Scheme 1b).[20]

Herein, we propose a concept of counterion-enhanced catalysis for the enantioselective α-allylation of α-branched aldehydes with allylic alcohols (Scheme 1c). The combination of simple chiral amines together with readily prepared achiral

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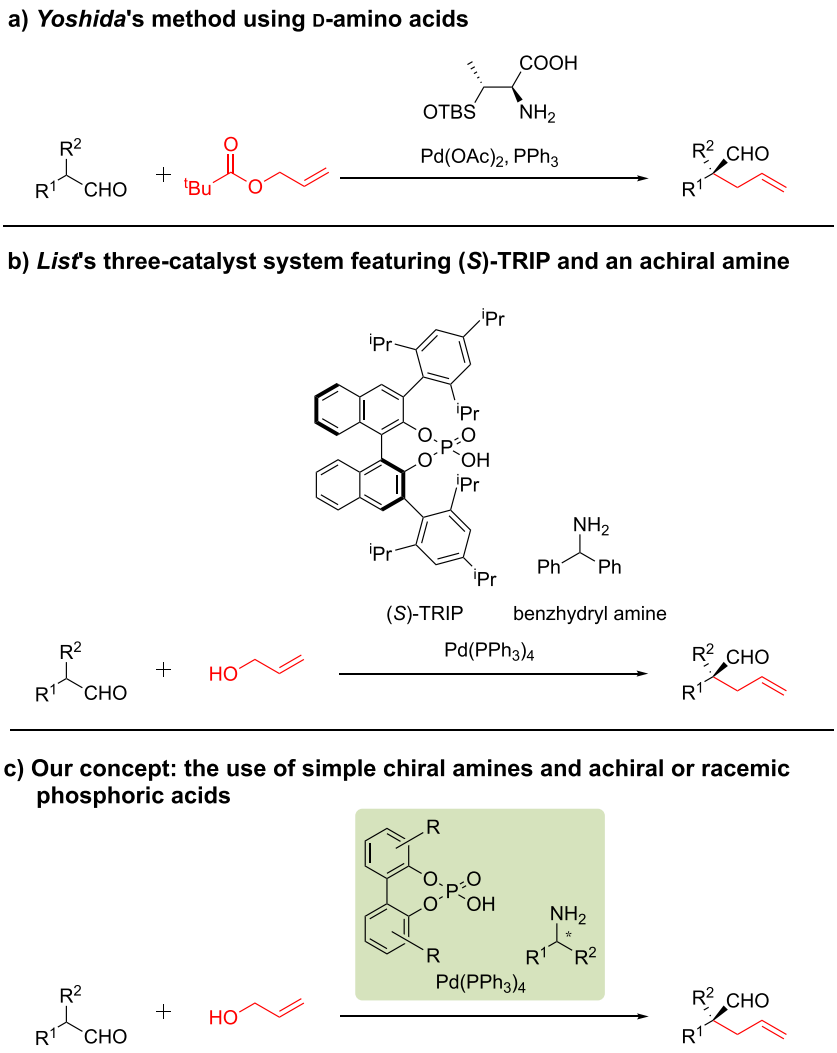
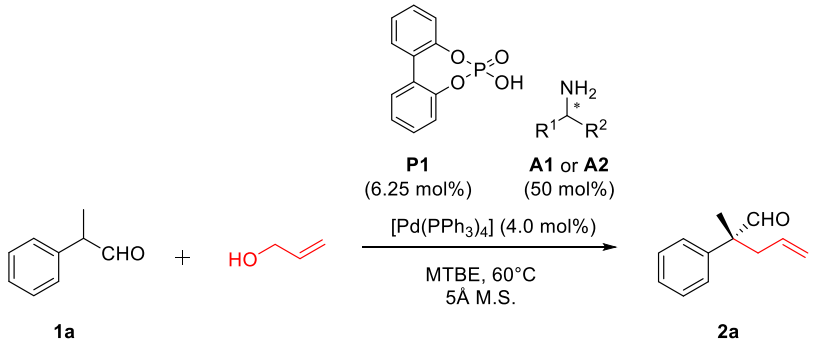
Scheme 1. Concepts for the α-Allylation of Branched Aldehydes



Scheme 2. Asymmetric α-Allylation of 2-Phenylpropanal



or racemic phosphoric acids and $Pd(PPh_3)_4$ resulted in high catalytic activities and excellent stereocontrol. As no extensive catalyst preparation is required, this methodology could provide a good alternative to current state-of-the-art methods.

RESULTS AND DISCUSSION

To establish the new concept, we were initially interested in the asymmetric α-allylation of 2-phenylpropanal (**1a**). Based on our previous observations for asymmetric counterion-enhanced catalysis, L-valine *tert*-butyl ester (**A1**) was chosen as the amine source, together with the phosphoric acid **P1** (Scheme 2).[21] MTBE as an apolar aprotic solvent was used as its low dielectric constant might facilitate the formation of stronger contact ion pairs. In accordance with the relevant literature, high amine loadings were used.[20] After the initial screening for proper concentrations and desiccant, the product **2a** could be obtained in good yield, albeit with moderate enantioselectivity (Table 1, entry 1). Gratifyingly, the ee could be dramatically increased to 78% by simply changing the amine source to the C_2-symmetric diamine (*R*,*R*)-**A2**, also increasing

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Table 1. Initial Screening and Proof of Concept

entry[a]	amine	comment	yield (%)[b]	ee (%)[c]
1	(*S*)-**A1**		82	31 (*S*)
2			87	78 (*R*)
3	(*R*,*R*)-**A2**	0 mol % [$Pd(PPh_3)_4$]	0	n.d.
4		0 mol % **P1**	37	35 (*R*)
5		0 mol % (*R*,*R*)-**A2**	81	0

[a]Performed on a 0.375 mmol scale by using 4.0 mol % $Pd(PPh_3)_4$, 50 mol % amine, 6.25 mol % **P1**, 190 mg 5 Å molecular sieves, and 0.75 mmol allyl alcohol in 0.75 mL MTBE at 60 °C for 16 h. [b]Determined by gas chromatography (GC) analysis. [c]Determined by chiral high-performance liquid chromatography (HPLC) analysis using a Diacel Chiralcel AS-H column. Absolute configurations were determined by measuring the optical rotations and comparing with the literature data.

the yield (Table 1, entry 2). As can be seen, all three catalyst components are essential for achieving high catalytic activity and selectivity. In the absence of $Pd(PPh_3)_4$, the formation of **2a** could not be observed (Table 1, entry 3). Without the amine source, the reaction presumably follows a pure enol pathway catalyzed by the phosphoric acid **P1**, consequently resulting in a racemic product (Table 1, entry 5). Nevertheless, the use of the phosphoric acid was also found to be crucial, as both the reactivity and the selectivity drastically decrease in the absence of compound **P1** (Table 1, entry 4).

To further tune our catalytic system, a series of different achiral or racemic phosphoric acids have been synthesized following a straightforward one- or two-step reaction procedure using cheap and easily accessible phenols and bisphenols as starting materials. The use of **P1**–**P7** yielded the allylation product **2a** in high to excellent yields and enantioselectivity (Figure 1). The best result was obtained with the thymol-derived analogue **P5**, resulting in 98% yield and 94% ee. To investigate whether the stereochemistry of the racemic phosphoric acids plays a role in the reaction, the BINOL-derived acid **P8** was tested in the enantiopure form (both isomers) and also as a racemic mixture. In all three cases, product **2a** was obtained with basically the same enantioselectivity (73%), suggesting that match/mismatch scenarios between the chiral amine and the racemic phosphoric acid do not affect the degree of asymmetric induction. This is in good agreement with our previous observations for organocatalytic asymmetric transfer hydrogenations.[21] Furthermore, diphenyl phosphate as well as other Brønsted and Lewis acids traditionally used for organocatalysis were also tested. Only

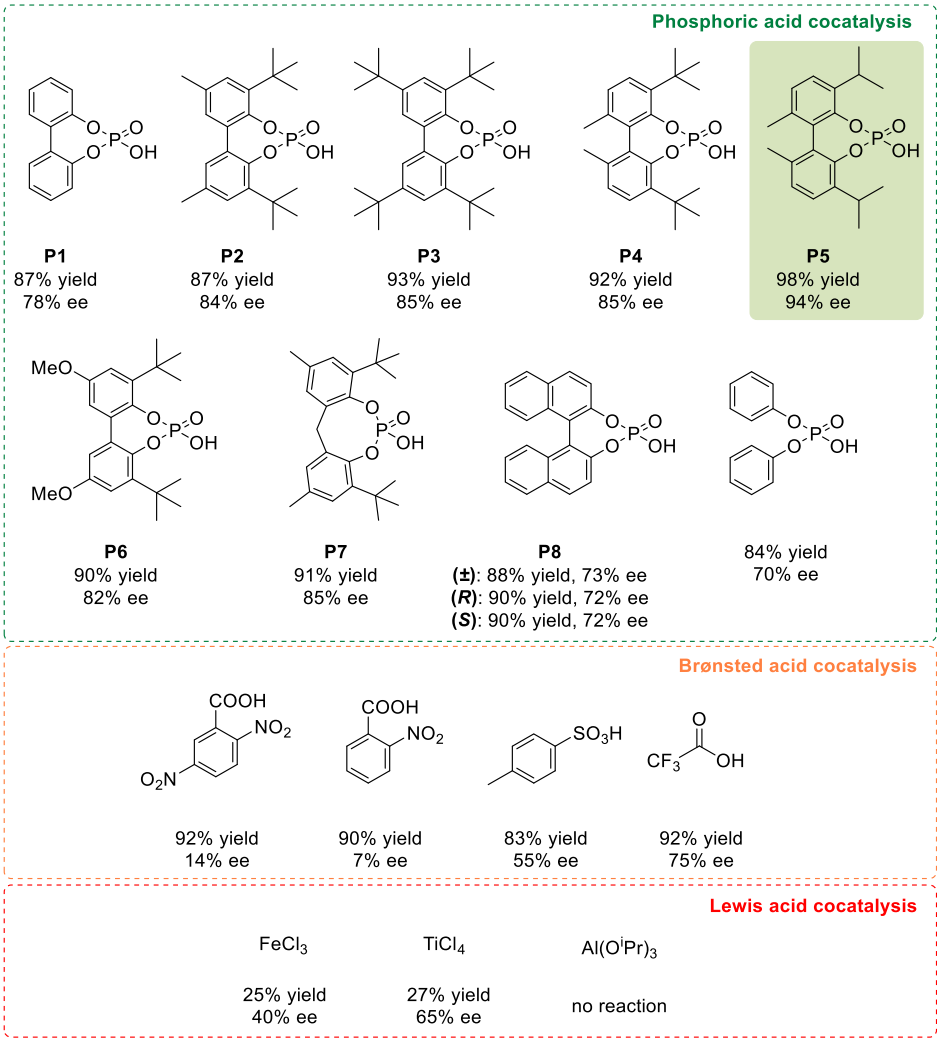

Figure 1. Effect of different acidic cocatalysts in the asymmetric α-allylation of **1a**. The reaction conditions were identical to those used in Table 1, entry 2.

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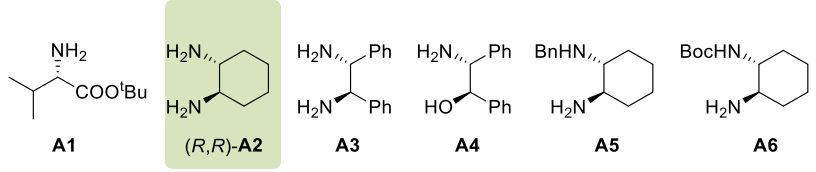
Table 2. Different Amines for the Asymmetric α-Allylation of 1a



entry[a]	amine	yield (%)[b]	ee (%)[c]
1	**A1**	89	31 (*S*)
2	(*R*,*R*)-**A2**	98	94 (*R*)
3	(*S*,*S*)-**A2**	97	94 (*S*)
4	**A3**	89	37 (*R*)
5	**A4**	89	21 (*R*)
6	**A5**	90	60 (*R*)
7	**A6**	97	44 (*R*)

[a]Performed on a 0.375 mmol scale by using 4.0 mol % $Pd(PPh_3)_4$, 50 mol % amine, 6.25 mol % **P5**, 190 mg 5 Å molecular sieves, and 0.75 mmol allyl alcohol in 0.75 mL MTBE at 60 °C for 16 h. [b]Determined by GC analysis. [c]Determined by chiral HPLC analysis using a Diacel Chiralcel AS-H column. Absolute configurations were determined by measuring the optical rotations and comparing with the literature data.

trifluoroacetic acid led to a comparable result of 75% ee; all others resulted in significantly inferior results, highlighting the particular advantages associated with the use of achiral or racemic phosphoric acids **P1**−**P7** (Figure 1, also see Supporting Information Tables S2 and S3, pages S4−S6).

Next, a small set of chiral amines (**A1**−**A6**) was screened. While the product **2a** was formed in high yields in all cases, the enantioselectivity was moderate when using an amine other than (*R*,*R*)-**A2** (Table 2). Presumably, the high rigidity of amine (*R*,*R*)-**A2** results in a significantly increased energy difference between the diastereomorphic transition states, therefore results in higher enantioselectivity.

Furthermore, by simply changing the amine source from (*R*,*R*)-**A2** to (*S*,*S*)-**A2**, the product (*S*)-**2a** could be obtained with the same excellent enantioselectivity of 94% ee (Table 2, entries 2−3). However, given the economic considerations, the (*R*,*R*)-**A2** analogue was used for further optimizations, as well as for investigating the scope and limitations.

With the suitable amine [(*R*,*R*)-**A2**] and phosphoric acid (**P5**) in hand, we sought to optimize the ratio of these two components. Eventually, we found that the selectivity of the product **2a** highly depends on the amine-to-acid ratio. As the allylic aldehyde **2a** was obtained in rather high yield even in the absence of the amine source (Table 1, entry 5), it is likely that the level of asymmetric induction is determined by competing enamine- and enol-mediated pathways (see the plausible key intermediates in Figure 2). Decreasing the amine-to-acid ratio leads to an increase in the enol-mediated product, consequently resulting in lower ee values (Figure 2, left side, see also Supporting Information Table S5, page S8). By increasing the amine-to-acid ratio, the level of asymmetric induction increases rapidly. Because of the higher nucleophilicity of the enamine, it can suppress the formation of the enol intermediate and, therefore, lead to an optically active product; however—in accordance with the observations of List—a rather high amine loading was necessary to achieve this. Based on the results, it seems that the initially used amine-to-acid ratio of 8:1 gives the best results (Figure 2, middle), while a further increase in the amine loading could possibly increase the free amine-to-enamine ratio to an undesired level: this would lead to the phosphoric acid reacting with the free amine rather than the enamine, thus hampering the selectivity (Figure 2, right side).

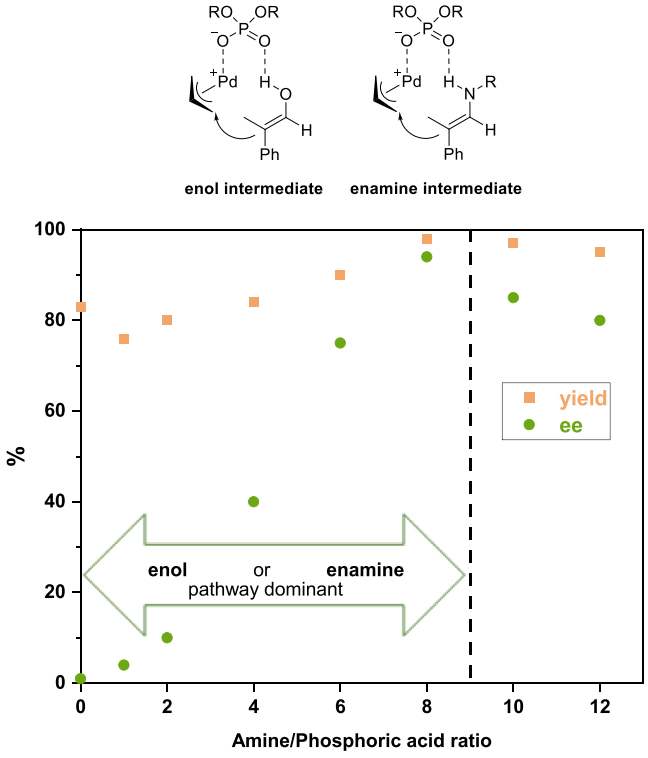


Figure 2. Effect of different amine-to-phosphoric acid ratios in the asymmetric α-allylation of **1a** using amine (*R*,*R*)-**A2** and phosphoric acid **P5** (bottom), and the plausibly competing key intermediates for the enol and enamine pathways (top).

Finally, the effect of the solvent was also investigated. Only slight differences in the catalytic activity and selectivity were observed (see Supporting Information Table S6, page S9) as the allylic aldehyde **2a** could be obtained in rather high yield and enantioselectivity even in green, bio-derived solvents like 2-MeTHF. Most importantly, the solvent screening showed that the use of toluene allowed both the reaction temperature and the catalyst loadings to be decreased successfully. However—similar to previous reports—a relatively high absolute amine loading was necessary to retain a high level of asymmetric induction.

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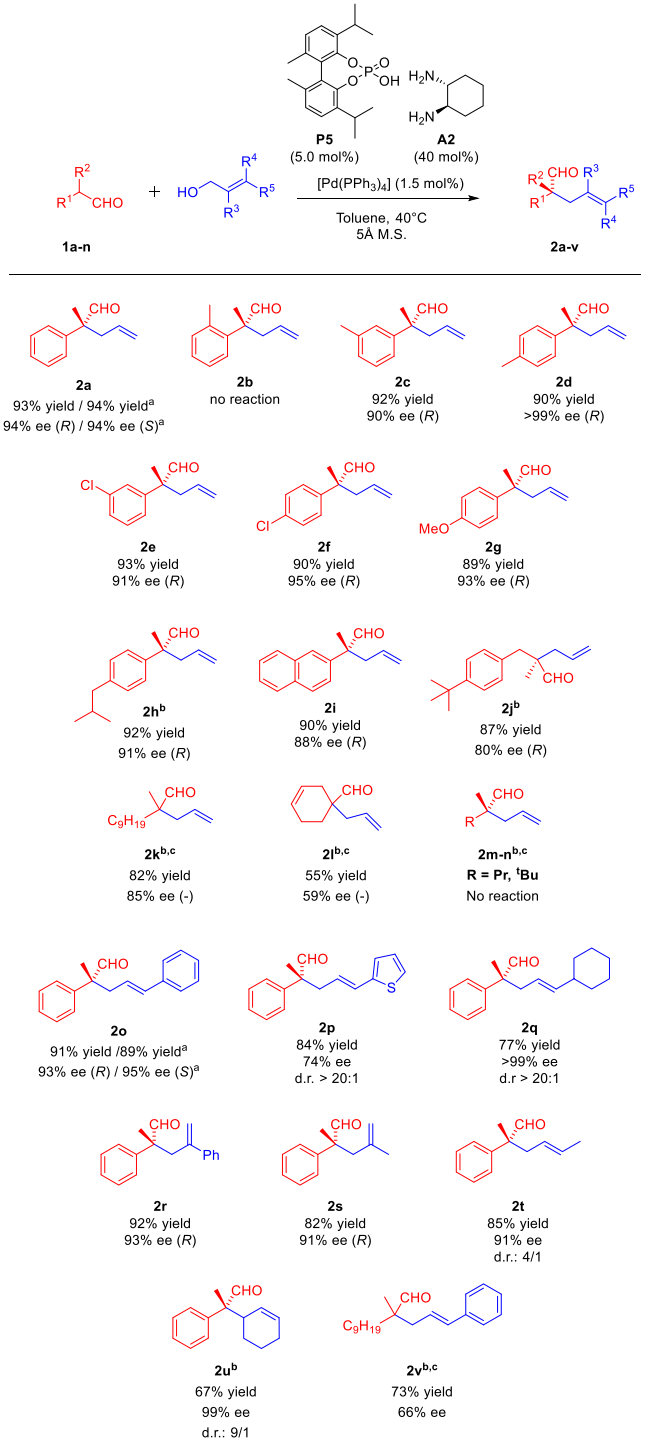
Having optimized and established the catalytic system, we explored the scope and limitations of the reaction by testing different α-branched aldehydes (Scheme 3). Electron-withdrawing and -donating groups in the meta and the para positions of the aryl group were well tolerated, resulting in high yields and enantioselectivity up to >99% ee for the allylic aldehydes **2c**–**j** under the previously optimized reaction conditions; however, no reaction was observed when using the ortho-substituted aldehyde **1b**. Eventually, we also tried to expand the scope to aliphatic aldehydes. Gratifyingly, both a linear and a cyclic aliphatic substrate could be allylated by simply increasing the temperature to 90 °C, yielding the corresponding products (**2k**–**l**) with moderate to high yield and enantioselectivity; even though still no reaction was observed for short-chained aliphatic aldehydes (**2m**–**n**).

Furthermore, our catalyst system was found to well tolerate different substituted allylic alcohols as well (Scheme 3). Aliphatic and aromatic primary allylic alcohols readily furnished the corresponding products (**2o**, **2r**–**2t**) in good to excellent yield and in excellent enantiopurity. Moreover, acyclic and cyclic secondary allylic alcohols were also found to be suitable reagents for the synthesis of **2p**–**q** and **2u**, with the first two resulting in the rearranged, linear allylic aldehydes **2p** and **2q** as major products (Scheme 3). Our procedure could also give an easy access to both product enantiomers: when using (*S*,*S*)-**A2** for the allylation of **1a** with allyl alcohol and cinnamyl alcohol, the (*S*)-product antipodes [(*S*)-**2a** and (*S*)-**2o**] could be obtained with the same excellent 94 and 95% ee, respectively (Scheme 3).

The proposed reaction mechanism comprises three catalytic cycles (Figure 3). In the enamine cycle (marked with red), the substrate **1a** reacts with the free amine (*R*,*R*)-**A2** to form the enamine **I**. The allylpalladium–π complex **II** is generated in the second catalytic cycle (green) via acidic activation of the allylic alcohol and subsequent oxidative addition to the Pd^0 species. The enamine intermediate **I** is then allylated with complex **II** through the key intermediate **III** involving all three catalyst components. This is then dissociated, resulting in the formation of the imine **IV**, meanwhile the phosphoric acid and the Pd^0 are regenerated (green and orange cycles). Finally, hydrolysis of imine **IV** yields the product **2a**. Alternatively, the free amine (*R*,*R*)-**A2** could also be allylated directly to give **VI**; however—given the high catalytic efficiency—this must dissociate as the reaction proceeds. Based on our observations and in accordance with the literature, a rather high amine loading is necessary.[20] We suspect that the hydrolysis of the imine **IV** is rather slow, therefore a relatively high amine loading is necessary to speed it up and thus ensure that the enamine pathway outperforms the competing enol-mediated reaction (see Figure 3). Our plausible mechanism is supported by analytical studies, as the mass of the enamine **I**, the imine **IV**, the allylpalladium–π complex **II**, and the activated allylic alcohol **V** intermediates could all be detected via electron spin ionization-mass spectrometry (ESI-MS) analysis (see Supporting Information page S67 for details). A similar study was carried out by using the amine **A1** via GC–MS analysis, resulting in the same type of proposed catalytic cycle (see Supporting Information pages S67–S70 for details).

Furthermore, the enantioenriched allylic aldehyde **2a** could be smoothly and orthogonally converted into the corresponding formate **3** and into the dicarbonyl compound **4** via Baeyer–Villiger oxidation and Wacker-oxidation, respectively, retaining the excellent enantioselectivity of **2a** (Scheme 4).

Scheme 3. Scope and Limitations in the Asymmetric α-Allylation of α-Branched Aldehydes[a]



[a]Reactions were performed on a 0.75 mmol scale by using 1.5 mol % $Pd(PPh_3)_4$, 40 mol % amine(*R*,*R*)-**A2**, 5.0 mol % **P5**, 190 mg 5 Å molecular sieves, and 1.50 mmol (substituted) allylic alcohol in 1.50 mL toluene at 40 °C for 16 h. Yields refer to pure products after isolation by flash column chromatography. The enantioselectivity was determined by chiral HPLC and chiral GC analysis. Absolute configurations were determined by measuring the optical rotations and comparing with the literature data. [a](*S*,*S*)-**A2**, as the amine source, resulting in the formation of (*S*)-**2a**. [b]A higher catalyst loading of 4.0 mol % $Pd(PPh_3)_4$, 50 mol % (*R*,*R*)-**A2**, and 6.25 mol % **P5** were used. [c]Reaction performed at 90 °C.

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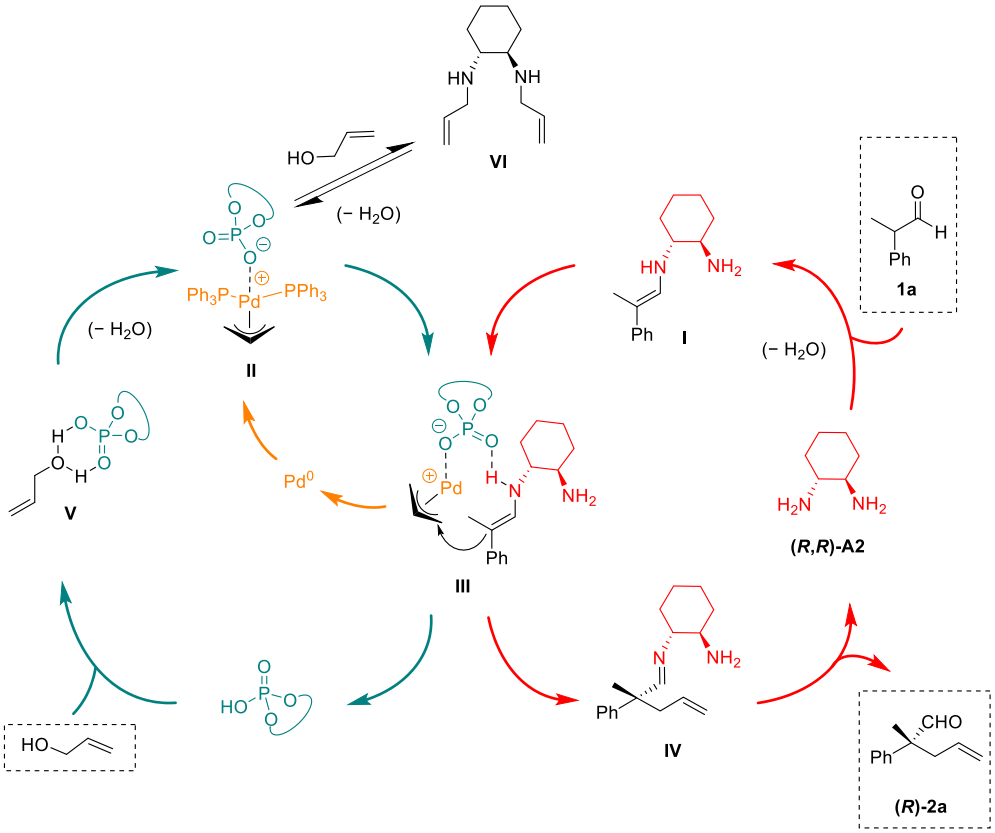
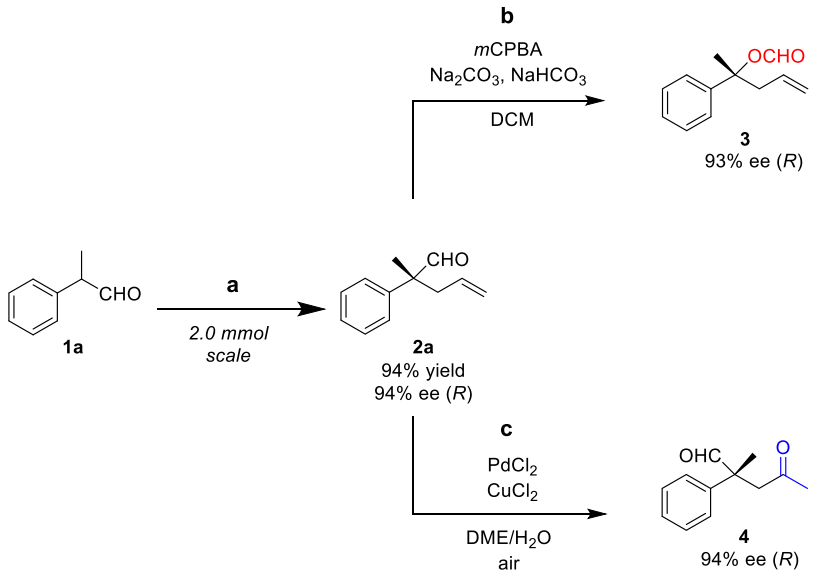


Figure 3. Plausible reaction mechanism for the direct α-allylation of α-branched aldehyde **1a** by using (*R*,*R*)-**A2**, phosphoric acid **P5** and $Pd(PPh_3)_4$. The product enantiomer generated in excess [(*R*)-**2a**] is illustrated in the cycle for clarity.

Scheme 4. Utilization of 2a for the Synthesis of the α-Branched Quaternary Allylic Formate 3 and Dicarbonyl Compound 4[a]



[a](a) Performed on a 2.0 mmol scale by using 40 mol % amine (*R*,*R*)-**A2**, 5.0 mol % **P5**, 1.5 mol % $Pd(PPh_3)_4$, 190 mg 5 Å molecular sieves, and 4.0 mmol allyl alcohol in 4.0 mL toluene at 40 °C for 16 h. Yield refers to pure **2a** after flash column chromatography. (b) Performed on a 1.0 mmol scale by using 2.1 mmol *m*CPBA, 1.5 mmol $NaHCO_3$, and 1.2 mmol Na_2CO_3 in anhydrous CH_2Cl_2 at 25 °C for 24 h. Purified by flash column chromatography. (c) Performed on a 0.9 mmol scale by using 0.09 mmol $PdCl_2$ and 0.09 mmol $CuCl_2$ in a mixture of DME and water (v/v 9/1). Purified by flash column chromatography.

CONCLUSIONS

Herein, we reported a concept of counterion enhanced Pd/enamine catalysis for the asymmetric α-allylation of α-branched aldehydes. Our multicomponent catalyst system relying on a commercially available chiral amine, a readily synthesized phosphoric acid, and $Pd(PPh_3)_4$ resulted in a simple and rather cheap chiral framework. The catalyst system was found to be quite versatile, tolerating different aromatic

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and aliphatic aldehydes, as well as substituted primary and secondary allylic alcohols. Furthermore, the possible orthogonal derivatization of the enantioenriched aldehydes was demonstrated through the synthesis of the α-branched quaternary allylic formate **3** and the dicarbonyl compounds **4**.

EXPERIMENTAL SECTION

General Experimental Information. All purchased chemicals from commercial suppliers were used without further purification. Dry solvents were predistilled and desiccated on aluminum oxide columns (PureSolv, Innovative Technology). Column chromatography was performed on standard manual glass columns using Merck (40−60 μm) silica gel with predistilled solvents (EtOAc: ethyl acetate, Et_2O: diethyl ether). For TLC analysis, precoated aluminum-backed plates were purchased from Merck (silica gel 60 F_{254}). UV-active compounds were detected at 254 nm. Non UV-active compounds were detected using Hanessian's stain solution (cerium molybdate stain). ^{1}H, ^{13}C, and ^{31}P nuclear magnetic resonance (NMR) spectra were recorded on a Bruker Advance UltraShield 200 or 400 MHz spectrometer, and chemical shifts are reported in ppm using TMS (tetramethylsilane) as the internal standard. Coupling constants (J) are given in Hz. The following abbreviations are used to explain multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), brs (broad singlet), dd (doublet of doublets), ddd (doublets of doublet of doublets), and td (triplet of doublets). GC measurements were performed on a Thermo Scientific Focus instrument, by using the BGB5 column and a flame ionization detector. Chiral HPLC measurements were carried out on a DIONEX ultraperformance liquid chromatograph equipped with a PDA plus detector (190−360 nm), using Diacel Chiralcel AS-H, OJ, or IB columns (250 × 4.60 mm, 5 μm). Chiral GC measurements were carried out on a Thermo Scientific Focus instrument, by using a BGB173 column and a flame ionization detector. To determine the absolute configuration, optical rotation was measured on an Anton Paar MCP500 polarimeter under the specific conditions and the results were compared to literature values. Concentrations are given in g/100 mL. High-resolution MS analysis was performed using a HTC PAL system autosampler, an Agilent 1100/1200 high-performance liquid chromatograph, and an Agilent 6230 AJS ESI-time-of-flight mass spectrometer. Microwave reactions were performed in a Biotage Initiator Classic microwave reactor in sealed, 20 ml pressure tight glass vials. Infrared (IR) spectra were recorded on a PerkinElmer Spectrum 65 Fourier transform IR spectrometer equipped with a specac MK II Golden Gate Single Reflection ATR unit.

Amine(*S*)-**A1**, (*R*,*R*)-**A5**, and (*R*,*R*)-**A6** were prepared according to literature procedures.[22−24]

General Procedures for the Phosphoric Acid Synthesis. Phosphoric acids **P1**, **P7**, and **P8** were prepared by direct phosphorylation of the corresponding diols.[25] Phosphoric acids **P2**−**P6** were prepared in a two-step fashion via oxidative coupling of the corresponding phenols (method A or B) followed by subsequent phosphorylation.[26−28]

*4,8-Di-tert-butyl-6-hydroxy-2,10-dimethyldibenzo[d,f]-[1,3,2]-dioxaphosphepine 6-oxide (**P2**) (Method A).* In a pressure-tight MW-vial, 2-(*tert*-butyl)-4-methylphenol (1.5 g, 12.0 mmol, 1.0 equiv) was dissolved in chlorobenzene (7.2 mL, 1.66 M solution) and di-*tert*-butyl peroxide (2.3 mL, 12.6 mmol, 1.05 equiv) was added. The vial was sealed, and it was stirred for 15 min at room temperature. The vial was then placed in a microwave reactor and the reaction mixture was stirred for 15 min (160 °C, high absorption setting and 10 bar pressure limit to avoid safety issues). The reaction mixture was allowed to cool down, and volatiles were removed in vacuo. Column chromatography (silica gel, 1.5% EtOAc in light petrol) afforded 3,3′-di-*tert*-butyl-5,5′-dimethyl-[1,1′-biphenyl]-2,2′-diol as a pale yellow solid (845 mg, 56% yield). To the solution of this diol (800 mg, 2.45 mmol, 1.0 equiv) in pyridine (7 mL), $POCl_3$ (0.51 mL, 5.4 mmol, 2.2 equiv) was slowly added via a syringe at 0 °C. The reaction mixture was stirred for 24 h at 95 °C (heating mantle, IKA). After being cooled down to room temperature, distilled H_2O (4 mL) was added, and the resulting clear solution was stirred for another 18 h at 95 °C (heating mantle, IKA). After cooling down to room temperature, 4 N HCl (25 mL) was slowly added. The precipitate was filtered off, and it was washed with 4 N HCl. The product was further washed and hydrolyzed by redissolving it in CH_2Cl_2 and washing several times with 4 N HCl. After being dried over Na_2SO_4, removal of the solvent yielded the phosphoric acid **P2** as a lightly grayish solid (630 mg, 66% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.48 (br s, 1H, POO*H*), 7.26 (s, 2H, *H*-arom), 7.02 (s, 2H, *H*-arom), 2.36 (s, 6H, 2× CH_3), 1.50 (s, 18H, 6× CH_3−C); ^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) 0.48. Analytical data were in accordance with the literature.

*2,4,8,10-Tetra-tert-butyl-6-hydroxydibenzo[d,f][1,3,2]-dioxaphosphepine 6-oxide (**P3**) (Method B).* A solution of 3-*tert*-butyl-4-hydroxyanisole (2.47 g, 12.0 mmol, 1.0 equiv) in methanol (75 mL) was prepared and a solution of KOH (2.77 g, 49.0 mmol, 4.1 equiv) and $K_3Fe(CN)_6$ (4.58 g, 14.0 mmol, 1.17 equiv) in water (75 mL) was added dropwise over 1 h at room temperature. The mixture was stirred for 2 h before the addition of 50 mL of water. The suspension was extracted with ethyl acetate (3 × 50 mL) and the combined organic phases were washed with brine. After being dried over Na_2SO_4, removal of the solvents under reduced pressure afforded a light brown solid. After washing with *n*-hexane, 3,3′,5,5′-tetra-*tert*-butyl-[1,1′-biphenyl]-2,2′-diol was obtained as an off-white powder (1.80 g, 73% yield). The subsequent phosphorylation was carried out according to the synthesis of **P2** on a 4.4 mmol scale, yielding phosphoric acid **P3** as an off-white solid (1.97 g, 95% yield). HRMS [(ESI-time-of-flight (TOF)] m/z: $[M + Na]^+$ calcd for $C_{28}H_{41}O_4PNa$, 495.2640; found, 495.2640; IR ATR (ν_{max}/cm^{-1}): 2955 (O−H), 2867 (C−H), 1615 (C═C), 1302 (C−O), 1025 (C−H), 899 (C−H arom), 701 (C−H arom); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.57 (br s, 1H), 7.42 (br s, 2H), 7.12 (d, J = 2.0 Hz, 2H), 1.45 (s, 18H), 1.27 (s, 18H); ^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) 0.40; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 147.9, 144.3, 144.1, 140.2, 140.1, 130.1, 126.5, 125.3, 35.5, 34.7, 31.5, 31.3.

*4,8-Di-tert-butyl-6-hydroxy-1,11-dimethyldibenzo[d,f]-[1,3,2]-dioxaphosphepine 6-oxide (**P4**).* 3,3′-Di-*tert*-butyl-6,6′-dimethyl-[1,1′-biphenyl]-2,2′-diol was prepared via method A on a 12.0 mmol scale. Column chromatography (silica gel, 1.5% EtOAc in light petrol) afforded the diol as a white solid (910 mg, 45% yield). The subsequent phosphorylation was carried out according to the synthesis of **P2** on a 3.4 mmol scale, yielding phosphoric acid **P4** as a white solid (900 mg, 69% yield). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{29}O_4PNa$, 411.1701; found, 411.1732; IR ATR (ν_{max}/cm^{-1}): 2961 (O−H), 2872 (C−H), 1610 (C═C), 1308 (C−O), 1023 (C−H), 901 (C−H arom), 700 (C−H arom); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 7.38 (dd, J = 8.0, 1.5 Hz, 2H), 7.11 (dd, J = 11.8, 8.2 Hz, 2H), 2.01 (d, J = 27.3 Hz, 6H), 1.48 (d, J = 12.4 Hz, 18H); ^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) 3.99; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 144.5, 144.3, 140.8, 140.7, 134.8, 130.1, 129.9, 128.9, 35.2, 31.3, 21.1.

*6-Hydroxy-4,8-diisopropyl-1,11-dimethyldibenzo[d,f][1,3,2]-dioxaphosphepine-6-oxide (**P5**).* 3,3′-Diisopropyl-6,6′-dimethyl-[1,1′-biphenyl]-2,2′-diol was prepared via method A on a 20.0 mmol scale. Column chromatography (silica gel, 2.0% EtOAc in light petrol) afforded the diol as a pale yellow liquid (2.03 g, 68% yield). The subsequent phosphorylation was carried out according to the synthesis of **P2** on a 6.7 mmol scale, yielding phosphoric acid **P5** as an amorphous brown solid (2.0 g, 83% yield). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{20}H_{25}O_4PNa$, 383.1388; found, 383.1389; IR ATR (ν_{max}/cm^{-1}): 2963 (O−H), 2872 (C−H), 1610 (C═C), 1204 (C−O), 967 (C−H), 818 (C−H arom), 696 (C−H arom); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 8.24 (br s, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.15 (d, J = 8.0 Hz, 2H), 3.49−3.45 (m, 2H), 2.14 (s, 6H), 1.27 (dd, J = 25.5, 6.9 Hz, 12H); ^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) 2.40; ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ (ppm) 145.4, 137.7, 136.1, 128.0, 127.1, 126.3, 26.6, 24.1, 22.8, 19.7.

*4,8-Di-tert-butyl-6-hydroxy-2,10-dimethoxydibenzo[d,f]-[1,3,2]-dioxaphosphepine-6-oxide (**P6**).* 3,3′-Di-*tert*-butyl-5,5′-dimethoxy-[1,1′-biphenyl]-2,2′-diol was prepared according to literature procedure (method B) on a 4.0 mmol scale. The subsequent

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phosphorylation was carried out according to the synthesis of **P2** on a 0.8 mmol scale, yielding phosphoric acid **P6** as a light brown solid (300 mg, 89% yield). HRMS (ESI-TOF) m/z: $[M + Na]^+$ calcd for $C_{22}H_{29}O_6PNa$, 443.1599; found, 443.1595; IR ATR (ν_{max}/cm^{-1}): 2971 (O−H), 2870 (C−H), 1613 (C═C), 1210 (C−O), 1002 (C−H), 822 (C−H arom), 703 (C−H arom); ^1H NMR (400 MHz, $CDCl_3$): δ (ppm) 10.88 (br s, 1H), 6.96 (d, J = 2.0 Hz, 2H), 6.66 (d, J = 2.0 Hz, 2H), 3.74 (s, 6H) 1.42 (s, 18H); ^{31}P NMR (162 MHz, $CDCl_3$): δ (ppm) 1.64; $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 156.4, 142.7, 142.6, 140.4, 140.2, 131.0, 115.1, 113.0, 55.7, 35.5, 31.1.

General Procedure for Parameter Optimization. All reactions were carried out in flame-dried Schlenk tubes (25 mL, VWR) by using the standard Schlenk technique. A flame-dried Schlenk tube was charged with finely ground and freshly activated 5 Å molecular sieves (190 mg), $Pd(PPh_3)_4$ (17.3 mg, 0.015 mmol, 4.0 mol %), amine or amino-acid ester (50 mol %), phosphoric acid (6.25 mol %), and solvent (0.75 mL). Allyl alcohol (50 μL, 0.75 mmol, 2.0 equiv) and 2-phenylpropanal (50 μL, 0.375 mmol, 1.0 equiv) were added and the reaction mixture was stirred at the specific temperature for 16 h (in a preheated and stirred oil bath). Upon completion, Et_2O (3 mL) and 2 N HCl (5 mL) were added, and the reaction mixture was vigorously stirred for 30 min. A sample for GC and chiral HPLC analysis was taken to determine the yield and the enantioselectivity.

General Procedure for Scope and Limitation. A flame-dried Schlenk tube (25 mL, VWR) was charged with finely ground and freshly activated 5 Å molecular sieves (190 mg), $Pd(PPh_3)_4$ (13.0 mg, 0.01125 mmol, 1.5 mol %), (1*R*,2*R*)-diaminocyclohexane [(*R*,*R*)-**A2**, 34.2 mg, 0.30 mmol, 40 mol %], phosphoric acid **P5** (13.50 mg, 0.0375 mmol, 5.0 mol %), and toluene (1.5 mL). The corresponding allylic alcohol (1.5 mmol, 2.0 equiv) and aldehyde (0.75 mmol, 1.0 equiv) were added, and the reaction mixture was stirred at 40 °C for 16 h (in a preheated and stirred oil bath). Upon completion, Et_2O (6 mL) and 2 N HCl (10 mL) were added, and the mixture was vigorously stirred for 30 min. The reaction mixture was filtered through a short pad of Celite, and it was washed with Et_2O several times. The phases of the filtrate were separated, and the aqueous layer was extracted with Et_2O (2×). The combined organic phases were washed with water, dried over Na_2SO_4, and concentrated in vacuo. Purification by flash column chromatography (light petrol/Et_2O 15:1 or 9:1, UV and Henessian's stain visualization) afforded the pure products. The enantioselectivity was determined by chiral HPLC analysis.

*2-Phenyl-2-methylpent-4-enal (**2a**).*[19] Column chromatography (silica gel, light petrol/Et_2O 10:1) afforded **2a** as a colorless oil [(*R*)-enantiomer: 122 mg, 93% yield, 94% ee], [(*S*)-enantiomer: 124 mg, 94% yield, 94% ee]. $[\alpha]_D^{20}$ −69.0 (c 1.0, $CHCl_3$), [(*R*)-enantiomer] and +68.2 (c 1.0, $CHCl_3$), [(*S*)-enantiomer]; ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.40 (s, 1H), 7.23−7.11 (m, 5H), 5.55−5.34 (m, 1H), 4.98−4.89 (m, 2H), 2.58−2.52 (m, 2H), 1.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 201.9, 139.5, 133.2, 128.9, 127.2, 118.6, 53.6, 40.6, 18.5; chiral HPLC analysis: (Diacel Chiralcel AS-H column, *n*-heptane/2-propanol 99.8/0.2 v/v %, 1 mL/min, λ = 210 nm) t_R (*R*) = 21.2 min, t_R (*S*) = 26.0 min.

*(R)-2-(3-Methylphenyl)-2-methylpent-4-enal (**2c**).*[19] Column chromatography (silica gel, light petrol/Et_2O 10:1) afforded **2c** as a colorless oil (130 mg, 92% yield, 90% ee). $[\alpha]_D^{20}$ −75.1 (c 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm): 9.41 (s, 1H), 7.18−7.14 (m, 1H), 6.99−6.96 (m, 3H), 5.58−5.37 (m, 1H), 5.01−4.92 (m, 2H), 2.59−2.51 (m, 2H), 2.33 (s, 3H), 1.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 202.0, 139.4, 138.5, 133.3, 128.7, 128.1, 124.2, 118.5, 53.5, 40.6, 21.6, 18.8; chiral HPLC analysis: (Diacel Chiralcel AS-H column, *n*-hexane/2-propanol 99.8/0.2 v/v %, 1 mL/min, λ = 210 nm) t_R (*R*) = 8.1 min, t_R (*S*) = 9.6 min.

*(R)-2-(4-Methylphenyl)-2-methylpent-4-enal (**2d**).*[19] Column chromatography (silica gel, light petrol/Et_2O 12:1) afforded **2d** as a colorless oil (126 mg, 90% yield, >99% ee). $[\alpha]_D^{20}$ −61.3 (c 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.40 (s, 1H), 7.13−7.03 (m, 4H), 5.58−5.37 (m, 1H), 5.00−4.91 (m, 2H), 2.66−2.46 (m, 2H), 2.25 (s, 3H), 1.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 201.9, 140.1, 138.0, 133.7, 128.5, 128.3, 128.0, 124.2, 118.2, 52.8, 41.2, 22.3, 18.2; chiral HPLC analysis: (Diacel Chiralcel AS-H column, *n*-hexane/2-propanol 99.8/0.2 v/v %, 0.4 mL/min, λ = 210 nm) t_R (*R*) = 18.0 min, no minor enantiomer was detected.

*(R)-2-(3-Chlorophenyl)-2-methylpent-4-enal (**2e**).*[12] Column chromatography (silica gel, light petrol/Et_2O 10:1) afforded **2e** as a colorless oil (145 mg, 93% yield, 91% ee). $[\alpha]_D^{20}$ −65.5 (c 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm), 9.43 (s, 1H), 7.24−7.21 (m, 3H), 7.07−7.03 (m, 1H), 5.56−5.35 (m, 1H), 5.03−4.94 (m, 2H), 2.57−2.54 (m, 2H), 1.36 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 201.1, 141.7, 134.9, 132.6, 130.0, 127.6, 125.5, 119.1, 53.6, 40.6, 18.8; chiral HPLC analysis: (Diacel Chiralcel AS-H column, *n*-hexane/2-propanol 99.8/0.2 v/v %, 0.5 mL/min, λ = 210 nm) t_R (*S*) = 21.8 min, t_R (*R*) = 23.0 min.

*(R)-2-(4-Chlorophenyl)-2-methylpent-4-enal (**2f**).*[19] Column chromatography (silica gel, light petrol/Et_2O 10:1) afforded **2f** as a colorless oil (140 mg, 90% yield, 95% ee). $[\alpha]_D^{20}$ −72.1 (c 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.40 (s, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.11−7.07 (d, J = 8.0 Hz, 2H), 5.53−5.33 (m, 1H), 4.99−4.91 (m, 2H), 2.56−2.51 (m, 2H), 1.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 201.3, 138.0, 133.4, 132.7, 129.0, 128.6, 119.0, 53.2, 40.6, 18.9; chiral HPLC analysis: (Diacel Chiralcel OJ column, *n*-heptane/2-propanol 99.8/0.2 v/v %, 0.7 mL/min, λ = 235 nm) t_R (*R*) = 20.1 min, t_R (*S*) = 22.2 min.

*(R)-2-Methyl-2-(4-methoxyphenyl)pent-4-enal (**2g**).*[18] Column chromatography (silica gel, light petrol/Et_2O 8:1) afforded **2g** as a colorless oil (136 mg, 89% yield, 93% ee). $[\alpha]_D^{20}$ −58.1 (c 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.38 (s, 1H), 7.09 (d, J = 10.0 Hz, 2H), 6.83 (d, J = 10.0 Hz, 2H), 5.58−5.41 (m, 1H), 5.01−4.93 (m, 2H), 3.72 (s, 3H), 2.58−2.56 (m, 2H), 1.34 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 210.9, 158.8, 133.3, 131.2, 128.3, 118.5, 114.2, 55.2, 52.9, 40.5, 18.9; chiral HPLC analysis: (Diacel Chiralcel AS-H column, *n*-hexane/2-propanol 99.5/0.5 v/v %, 1.0 mL/min, λ = 235 nm) t_R (major) = 10.9 min, t_R (minor) = 11.8 min.

*(R)-2-(4-Isobutylphenyl)-2-methylpent-4-enal (**2h**).*[19] Column chromatography (silica gel, light petrol/Et_2O 13:1) afforded **2h** as a colorless oil (158 mg, 92% yield, 91% ee). $[\alpha]_D^{20}$ −70.3 (c 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.42 (s, 1H), 7.07 (s, 4H), 5.58−5.38 (m, 1H), 5.01−4.92 (m, 2H), 2.59−2.54 (m, 2H), 2.38 (d, J = 8.0 Hz, 2H), 1.78 (sept., J = 8.0 Hz, 1H) 1.35 (s, 3H), 0.82 (d, J = 8.0 Hz, 6H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 202.0, 140.8, 136.6, 133.4, 129.6, 126.9, 118.4, 53.3, 44.9, 40.6, 30,1, 18.9; chiral HPLC analysis: (Diacel Chiralcel AS-H column, *n*-hexane/2-propanol 99.8/0.2 v/v %, 0.5 mL/min, λ = 235 nm) t_R (*R*) = 13.0 min, t_R (*S*) = 14.4 min.

*(R)-2-(Naphtalen-2-yl)-2-methylpent-4-enal (**2i**).*[19] Column chromatography (silica gel, light petrol/Et_2O 9:1) afforded **2i** as a colorless oil (151 mg, 90% yield, 88% ee). $[\alpha]_D^{20}$ −109.2 (c 1.0, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.45 (s, 1H), 7.73−7.58 (m, 4H), 7.37−7.21 (m, 3H), 5.55−5.34 (m, 1H), 4.99−4.88 (m, 2H), 2.75−2.52 (m, 2H), 1.42 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 201.9, 136.9, 133.5, 133.2, 132.5, 128.6, 128.1, 127.6, 126.4, 126.3, 125.0, 118.7, 53.8, 40.6, 19.0; chiral HPLC analysis: (Diacel Chiralcel AS-H column, *n*-hexane/2-propanol 99.8/0.2 v/v %, 1 mL/min, λ = 235 nm) t_R (*R*) = 15.9 min, t_R (*S*) = 18.4 min.

*(R)-2-(4-(tert-Butyl)benzyl)-2-methylpent-4-enal (**2j**).* Column chromatography (silica gel, light petrol/Et_2O 12:1) afforded **2j** as a colorless oil (160 mg, 87% yield, 80% ee). $[\alpha]_D^{20}$ −67.6 (c 1.0, $CHCl_3$); HRMS (ESI-TOF) m/z: $[M + H]^+$ calcd for $C_{17}H_{25}O$, 245.1905; found, 245.1902; IR ATR (ν_{max}/cm^{-1}): 3035 (C−H), 2965 (C−H arom), 2935 (C−H), 2160 (C═C alkene), 1718 (C═O), 1600 (C═C arom), 1495 (C−H), 1446 (C−H), 840 (C−H arom), 764 (C−H arom), 700 (C−H arom); ^1H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.52 (s, 1H), 7.19 (d, J = 4.0 Hz, 2H), 6.95 (d, J = 4.0 Hz, 2H), 5.77−5.56 (m, 1H), 5.05−4.97 (m, 2H), 2.70 (d, J = 12.0 Hz, 2H), 2.33−2.04 (m, 2H), 1.21 (s, 9H), 0.94 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 206.1, 149.4, 133.5, 133.1, 129.9, 125.1, 118.8, 50.1, 41.4, 39.9, 34.4, 31.4, 18.6; chiral HPLC analysis: (Diacel

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Chiralcel OJ column, *n*-heptane/2-propanol 99.8/0.2 v/v %, 0.7 mL/min, λ = 235 nm) t_R (major) = 11.4 min, t_R (minor) = 12.0 min.

*(−)-2-Allyl-2-methylundecanal (**2k**).* Column chromatography (silica gel, light petrol/Et_2O 50:1) afforded **2k** as a colorless oil (138 mg, 82% yield, 85% ee). $[\alpha]_D^{20}$ −10.2 (*c* 1.0, $CHCl_3$); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{29}O$, 225.2218; found, 225.2210; IR ATR (ν_{max}/cm^{-1}): 2923 (C−H arom), 2854 (C−H), 1727 (C═O), 1456 (C−H), 1191 (C−H), 840 (C−H arom); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.39 (s, 1H), 5.69−5.59 (m, 1H), 5.03−4.96 (m, 2H), 2.22−2.05 (m, 2H), 1.39−1.38 (m, 2H), 1.26−1.10 (m, 14H) 0.95 (s, 3H), 0.81 (t, *J* = 6.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 206.4, 133.2, 118.3, 72.15, 49.0, 39.6, 35.3, 31.9, 30.2, 29.5, 29.3, 23.9, 22.7, 18.4, 14.1; chiral GC analysis (BGB 173 column, 160 °C isothermal 70 min, 30 °C/min to 220 °C) t_R (major) = 70.3 min, t_R (minor) = 71.6 min.

*(−)-1-Allylcyclohex-3-ene-1-carbaldehyde (**2l**).*[29] Column chromatography (silica gel, light petrol/Et_2O 20:1) afforded **2l** as a colorless oil (62 mg, 55% yield, 59% ee). $[\alpha]_D^{20}$ −5.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.42 (s, 1H), 5.68−5.60 (m, 3H), 5.02−4.97 (m, 2H), 2.28−2.14 (m, 3H), 2.00−1.94 (m, 2H), 1.88−1.80 (m, 2H), 1.54−1.47 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 205.8, 132.7, 126.8, 124.4, 118.6, 47.9, 39.8, 29.5, 27.0, 22.0; chiral HPLC analysis: (Diacel Chiralcel OJ column, *n*-hexane/2-propanol 99.5/0.5 v/v %, 0.3 mL/min, λ = 235 nm) t_R (minor) = 14.4 min, t_R (major) = 15.3 min.

*(E)-2,5-Diphenylpent-2-methyl-4-enal (**2o**).*[19] Column chromatography (silica gel, light petrol/Et_2O 10:1) afforded **2o** as a colorless oil [(*R*)-enantiomer: 170 mg, 91% yield, 93% ee], [(*S*)-enantiomer: 167 mg, 89% yield, 95% ee]. $[\alpha]_D^{20}$ −100.2 (*c* 1.0, $CHCl_3$), [(*R*)-enantiomer] and +101.0 (*c* 1.0, $CHCl_3$), [(*S*)-enantiomer]; ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.46 (s, 1H), 7.34−7.09 (m, 10H), 6.30 (d, *J* = 16.0 Hz, 1H), 5.92−5.76 (m, 1H), 2.73−2.66 (m, 2H), 1.39 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 202.0, 139.5, 137.2, 133.6, 129.0, 128.5, 127.5, 127.3, 127.2, 126.2, 123.4, 54.1, 39.9, 19.0; chiral HPLC analysis: (Chiralcel AS-H column, *n*-hexane/2-propanol 99/1 v/v %, 1 mL/min, λ = 210 nm) t_R (*R*) = 9.8 min, t_R (*S*) = 12.0 min.

*(R,E)-2-Methyl-2-phenyl-5-(thiophen-2-yl)pent-4-enal (**2p**).*[16] Column chromatography (silica gel, light petrol/Et_2O 15:1) afforded **2p** as a light yellow oil. (162 mg, 84% yield, 74% ee), ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.46 (s, 1H), 7.33−7.30 (m, 2H), 7.24−7.17 (m, 3H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.83−6.81 (m, 1H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.42 (d, *J* = 16.0 Hz, 1H), 5.73−5.65 (m, 1H), 2.69−2.66 (m, 2H), 1.40 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 201.8, 142.3, 139.3, 130.0, 129.0 127.5, 127.2, 126.7, 124.9, 123.7, 54.1, 39.9, 18.9; chiral HPLC analysis: (Chiralcel AS-H column, *n*-heptane/2-propanol 93/7 v/v %, 1 mL/min, λ = 254 nm) t_R (*R*) = 6.6 min, t_R (*S*) = 7.6 min.

*(R,E)-5-Cyclohexyl-2-methyl-2-phenylpent-4-enal (**2q**).*[16] Column chromatography (silica gel, light petrol/Et_2O 15:1) afforded **2q** as a colorless oil (148 mg, 77% yield, >99% ee). ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.45 (s, 1H), 7.32−7.05 (m, 5H), 5.34−5.28 (m, 1H) 5.07−5.04 (m, 1H), 2.52−2.50 (m, 2H), 1.78−1.50 (m, 6H), 1.33 (s, 3H), 1.11−1.07 (m, 4H), 0.93−0.90 (m, 1H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 202.4, 141.0, 140.0, 128.8, 127.2, 121.6, 54.0, 40.8, 39.4, 33.1, 26.1, 19.0; chiral HPLC analysis: (Chiralcel AS-H column, *n*-heptane/2-propanol 99.8/0.2 v/v %, 1 mL/min, λ = 210 nm) t_R (major) = 17.5 min, no minor enantiomer was detected.

*(R)-2-Methyl-2,4-diphenylpent-4-enal (**2r**).*[29] Column chromatography (silica gel, light petrol/Et_2O 10:1) afforded **2r** as a colorless oil (173 mg, 92% yield, 93% ee). $[\alpha]_D^{20}$ −93.6 (*c* 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.34 (s, 1H), 7.20−7.09 (m, 10H), 5.10 (s, 1H), 4.80 (s, 1H) 3.19 (d, *J* = 12.0 Hz, 1H) 4.80 (d, *J* = 12.0 Hz, 1H), 1.24 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 201.4, 145.0 142.3, 139.5, 128.6, 128.2, 127.4, 127.2, 126.6, 117.7, 54.4, 41.7, 18.9; chiral HPLC analysis (Chiralcel IB column, *n*-hexane/2-propanol 99.5/0.5 v/v %, 1 mL/min, λ = 235 nm) t_R (*S*) = 7.0 min, t_R (*R*) = 7.8 min.

*(R)-2-Phenylpent-2,4-dimethyl-4-enal (**2s**).*[30] Column chromatography (silica gel, light petrol/Et_2O 15:1) afforded **2s** as a colorless oil (116 mg, 82% yield, 91% ee). $[\alpha]_D^{20}$ −51.8 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.47 (s, 1H), 7.33−7.19 (m, 5H), 4.73 (s, 1H), 4.54 (s, 1H) 2.61 (dd, *J* = 20 Hz, 14 Hz, 2H), 1.39 (s, 3H), 1.33 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 202.3, 139.9 129.2, 128.8, 127.2, 125.4, 53.9, 39.3, 19.1, 17.9; chiral HPLC analysis: (Chiralcel AS-H column, *n*-hexane/2-propanol 99.8/0.2 v/v %, 0.5 mL/min, λ = 210 nm) t_R (*R*) = 18.1 min, t_R (*S*) = 23.6 min.

*2-Phenylhex-2-methyl-4-enal (**2t**).*[19] Column chromatography (silica gel, light petrol/Et_2O 15:1) afforded **2t** as a colorless oil (120 mg, 85% yield, dr.: 4/1, 34% ee/91% ee). ^{1}H NMR (200 MHz, $CDCl_3$, major diast.): δ (ppm) 9.42 (s, 1H, C*H*O), 7.28−7.13 (m, 5H, *H*-arom), 5.45−5.37 (m, 1H), 5.14−5.02 (m, 1H), 2.53−2.49 (m, 2H), 1.50 (d, *J* = 8.0 Hz, 3H), 1.32 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$, major diast.): δ (ppm) 202.3, 139.9, 129.2, 128.8, 127.2, 125.4, 53.9, 39.3, 19.1, 17.9; chiral HPLC analysis: (Chiralcel AS-H column, *n*-hexane/2-propanol 99.8/0.2 v/v %, 0.5 mL/min, λ = 210 nm) t_R (minor diast.) = 13.9 min, 14.4 min, t_R (major diast.) = 16.2 min, 18.1 min.

*2-Phenyl-2-(cyclohex-2-en-1-yl)propanal (**2u**).*[29] Column chromatography (silica gel, light petrol/Et_2O 20:1) afforded **2u** as a colorless oil (108 mg, 67% yield, dr.: 9/1, 43% ee/99% ee). ^{1}H NMR (200 MHz, $CDCl_3$, major diast.): δ (ppm) 9.49 (s, 1H), 7.28−7.16 (m, 5H), 5.72−5.46 (m, 1H), 5.40−5.05 (m, 1H), 3.06−3.01 (m, 1H), 1.86 (br s, 2H), 1.71−1.01 (m, 7H); ^{13}C NMR (100 MHz, $CDCl_3$, major diast.): δ (ppm) 202.7, 139.2, 130.0, 128.8, 127.7, 127.2, 126.7, 56.8, 41.0, 40.5, 24.9, 24.4, 14.9, 14.3; chiral HPLC analysis: (Chiralcel AS-H column, *n*-hexane/2-propanol 99.8/0.2 v/v %, 0.5 mL/min, λ = 210 nm) t_R (minor diast.) = 19.3 min, 23.3 min, t_R (major diast.) = 20.7 min, 29.1 min.

*(R)-2-Cinnamyl-2-methylundecanal (**2v**).* Column chromatography (silica gel, light petrol/Et_2O 50:1) afforded **2v** as a colorless oil (164 mg, 73% yield, 66% ee). $[\alpha]_D^{20}$ −19.0 (*c* 1.0, $CHCl_3$); HRMS (ESI-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{21}H_{33}O$, 301.2531; found, 301.2535; IR ATR (ν_{max}/cm^{-1}): 2923 (C−H arom), 2853 (C−H), 1702 (C═O), 1184 (C−H), 700 (C−H arom); ^{1}H NMR (400 MHz, $CDCl_3$): δ (ppm) 9.45 (s, 1H), 7.27−7.14 (m, 5H), 6.35 (d, *J* = 16.0 Hz, 1H), 6.05−5.97 (m, 1H), 2.37−2.25 (m, 2H), 1.48−1.41 (m, 2H), 1.26−1.12 (m, 14H) 1.00 (s, 3H), 0.81 (t, *J* = 6.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 206.4, 137.2, 133.4, 128.5, 127.3, 126.1, 124.9, 49.6, 38.8, 35.5, 31.9, 30.2, 29.5, 29.3, 24.0, 22.7, 18.7, 14.1; chiral HPLC analysis: (Chiralcel OJ column, *n*-hexane/2-propanol 98/2 v/v %, 1 mL/min, λ = 254 nm) t_R (*R*) = 6.2 min, t_R (*S*) = 8.3 min.

Derivatization of the Enantioenriched Product 2a. *Synthesis of 2-Phenyl-2-methylpent-4-enal (**2a**) on 2.0 mmol Scale.* The synthesis was carried out in accordance with the general procedure for scope and limitation in a 50 mL VWR Schlenk tube (in a preheated and stirred oil bath). The reaction mixture was stirred at 40 °C for 16 h. The standard work-up procedure and the subsequent column chromatographic purification yielded the product **2a** as a colorless oil (332 mg, 95% yield), which was used quantitively for the synthesis of **3** and **4**, respectively.

*(R)-2-Phenylpent-4-en-2-yl Formate (**3**).* Prepared according to the literature procedure.[31] To a solution of the enantioenriched allylic aldehyde **2a** (174.5 mg, 1.0 mmol) in anhydrous CH_2Cl_2 (15 mL), *m*CPBA (70% assay, 394 mg, 2.10 mmol, 2.10 equiv), $NaHCO_3$ (138 mg, 1.50 mmol, 1.50 equiv), and Na_2CO_3 (138 mg, 1.20 mmol, 1.20 equiv) were added, and the resulting suspension was stirred for 24 h at room temperature. The reaction mixture was diluted with 10% $NaHCO_3$ and CH_2Cl_2 and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 (3×), and the combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated in vacuo. Flash column chromatography (light petrol/Et_2O 95:5) afforded the product 3 as a colorless liquid (152 mg, 80% yield, 93% ee). $[\alpha]_D^{20}$ −55.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 7.98 (s, 1H), 7.29−7.17 (m, 5H), 5.61−5.44 (m, 1H), 5.03−4.85 (m, 2H), 2.83−2.63 (m, 2H), 1.78 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 160.2, 143.6, 132.3, 128.4, 127.4,

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124.9, 119.1, 84.2, 46.8, 25.1; chiral HPLC analysis: (Chiralcel IB column, *n*-hexane/2-propanol 99.8/0.2 v/v %, 1 mL/min, λ = 210 nm) t_R (*R*) = 8.8 min, t_R (*S*) = 9.3 min.

(R)-2-Methyl-4-oxo-2-phenylpenatal (4). Prepared according to the literature procedure.[32] To a solution of the enantioenriched allylic aldehyde **2a** (157.0 mg, 0.9 mmol, 1.0 equiv) in a mixture of H_2O and dimethoxyethane (4.5 mL, 1/9 v/v) was added $PdCl_2$ (15.9 mg, 0.09 mmol, 0.1 equiv) and $CuCl_2$ (12.1 mg, 0.09 mmol, 0.1 equiv) and the resulting suspension was stirred overnight. The solvent was evaporated in vacuo and the crude product was purified by flash column chromatography (light petrol/EtOAc 5:1) affording the product 4 as a light yellow oil (124 mg, 72% yield, 94% ee). $[\alpha]_D^{20}$ −66.0 (*c* 1.0, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): δ (ppm) 9.49 (s, 1H), 7.31−7.16 (m, 5H), 3.04 (dd, *J* = 26.0 Hz, 18.0 Hz, 2H), 2.00 (s, 3H), 1.54 (s, 3H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ (ppm) 206.0, 201.0, 139.2, 129.0, 127.5, 126.8, 51.8, 50.4, 30.9, 19.9; chiral HPLC analysis: (Chiralcel IB column, *n*-hexane/2-propanol 95/5 v/v %, 1 mL/min, λ = 220 nm) t_R (*S*) = 10.3 min, t_R (*R*) = 11.8 min.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.0c02385.

Detailed parameter optimization, NMR spectra, and chiral HPLC traces (PDF)

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Notes

The authors declare no competing financial interest.

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