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Carvone-Derived P-Stereogenic Phosphines: Design, Synthesis, and Use in Allene–Imine [3 + 2] Annulation

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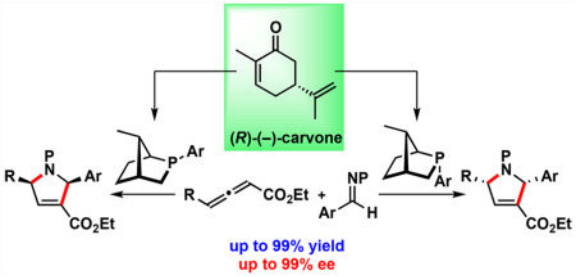
Abstract

We have prepared a previously unreported family of P-stereogenic [2.2.1] bicyclic chiral phosphines through straightforward syntheses starting from the natural product carvone. This design rationale prompted the development of an unforeseen C-dealkenylation reaction. We have applied these organocatalysts in the asymmetric syntheses of a bevy of pyrrolines, obtained in high yields and enantioselectivities, including a biologically active small molecule, efsevin.

Graphical abstract



Keywords

phosphine; organocatalysis; enantioselective; carvone; annulation; chiral pool; heterocycle

Chiral phosphines play significant roles in asymmetric catalysis.[1] These chiral ligands are typically divided into three design archetypes: (i) phosphines possessing stereogenic phosphorus centers (e.g., DIPAMP),[1a] (ii) phosphines having axial chirality (e.g., BINAP),[1b]

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Supporting Information

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Experimental procedures and analytical data for all new compounds (PDF)

Crystallographic data for compound **3b** (CIF)

Crystallographic data for compound **3c** (CIF)

The authors declare no competing financial interest.

and (iii) phosphines featuring carbon stereocenters (e.g., DuPhos, DIOP).[1c] Although phosphines possessing both carbon and phosphorus stereocenters have been particularly useful in asymmetric catalysis,[2] efficient methodologies for the production of enantiomers of C-and P-chirogenic phosphines remain scarce.[3] Herein we report the design, synthesis, and application of new rigid P-stereogenic phosphines derived from the monoterpenoid natural product carvone. These phosphines contain four to six stereogenic centers, one of which appears at the phosphorus center.

By harnessing chirality found in Nature, we realized our design starting from the terpenoid carvone, which has been used in many natural product syntheses[4] but seldom in the preparation of chiral ligands.[5] Here we decided to feature the [2.2.1] bicyclic scaffold found in our group's previously disclosed L-hydroxyproline (Hyp)-derived chiral phosphines,[6] the utility of which has been demonstrated in a number of recent synthetic applications.[7] Unlike Hyp, both antipodes of carvone are available from natural sources, allowing the facile generation of either enantiomeric product of chiral ligands through asymmetric transformations.

We envisioned that alkylation of the dimesylate **2** (derived from the known diol **1**)[8] would afford the [2.2.1] bicyclic scaffold of the phosphine **4a** (Scheme 1). The 2-propenyl motif would presumably control the stereochemistry at the newly formed phosphorus center and provide a handle for structural diversification. In the event, mesylation of the diol **1**, alkylation with dilithium phenylphosphide, and oxidation smoothly produced the phosphine oxide **3a**. This common intermediate provided access to the phosphine oxides **3b** (after hydrogenation with Wilkinson's catalyst), **3c** (after Sharpless asymmetric dihydroxylation), and **3d** (after Simmons–Smith cyclopropanation). Subsequent reductions with trichlorosilane gave the corresponding tertiary phosphines **4a**–**4d** in high yields.

To gauge the levels of asymmetric induction, we employed these chiral phosphines in [3 + 2] annulations of the allenoates **5** and *N*-(*p*-toluenesulfonyl)imine **6a** to form the pyrroline carboxylates **7** (Table 1).[9] Optimization of the reaction parameters led to the best results being obtained at room temperature when using benzene as the solvent and a 15 mol % catalyst loading.[10] Preliminary screening of the reaction of **6a** with the simple allenoate **5a** mediated by the 2-propenylsubstituted phosphine **4a** provided the adduct **7aa** in excellent yield (95%) and with modest enantioselectivity (15% ee, entry 1). When employing allenoates with γ-substituents, we observed products with improved enantioselectivities and high selectivity for the cis-adduct (entries 2–4), particularly for the reaction of the γ-*tert*-butylallenoate **5e** mediated by the catalyst **4a** (82% ee, entry 5). When applying the 2-propylsubstituted phosphine **4b**, the enantioselectivity increased further (93% ee, entry 6), whereas the 1,2-dihydroxy-2-propyl-substituted phosphine **4c** gave the product with the lowest enantioselectivity (77% ee, entry 7). Interestingly, no products were obtained from the reaction catalyzed by the 1-methylcyclopropyl-substituted phosphine **4d** (entry 8).

With the promising behavior of the phosphine **4b**, we briefly surveyed the scope of both the imine and allenoate components in the enantioselective syntheses of 1,2,3,5-tetrasubstituted pyrrolines **7** (Table 2). The γ-*tert*-butyl-substituted allenoate **5e** was compatible with an array of imines, furnishing products with benzenesulfonyl (Bs; **7eb**, 92% ee) and *p*-

nitrobenzenesulfonyl (nosyl, Ns; **7ec**, 95% ee) protecting groups. Pyrrolines derived from arylimines bearing ortho- (**7ed**, 98% ee), meta-(**7ee**, 94% ee), and para-substituted (**7ef**, 92% ee) phenyl groups were also tolerated, as was a 2-thienyl imine (**7eg**, 92% ee).

The enantioselectivity abated significantly when we varied the size of the allenoate γ-substituent from ethyl to isopropyl to a hydrogen atom (**7ch**, 83% ee; **7da**, 39% ee; **7aa**, 35% ee), presumably due to pronounced steric repulsion in the TS leading to the minor *R*-enantiomer.[11] We observed a similar trend with the phosphine **4a**, as displayed in Table 1 (**7da**, 38% ee; **7aa**, 15% ee). To improve the enantioselectivity when employing allenoates with smaller γ-substituents, we turned our attention to the further modification of the rigid catalyst framework.

Tables 1 and 2 reveal that the catalyst **4a** provided lower overall enantioselectivities than those of the catalyst **4b**. We hypothesized that this behavior might be due to the less flexible sp_2-hybridized 2-propenyl group exerting a greater steric effect on the endoface of the bicyclic phosphine than did the 2-propyl group. As indicated through X-ray crystallographic analysis of the phosphine oxide **3b** (Scheme 1), free rotation positioned the methine hydrogen atom of the 2-propyl group near the phosphorus center.[12,13] Extension of this hypothesis suggested that crowding of the endoface of the catalyst, where the phosphorus atom forms a covalent bond to the allenoate, would be detrimental to subsequent formation of a favorable stereochemistry-determining transition state.[11] Consistent with this rationale is the lack of reactivity in the reaction catalyzed by the phosphine **4d**.

On the basis of this reasoning, we investigated methods for removing the endosubstituent from the scaffold. We were inspired by the fragmentation of α-alkoxy hydroperoxides pioneered by Schreiber (Scheme 2).[14] The original procedure involves $FeSO_4$-mediated generation of an oxygen radical from an α-alkoxy hydroperoxide, fragmentation to form a carbon radical, oxidative coupling with $Cu(OAc)_2$, and β-hydride elimination to form an alkene. Although this protocol did not provide the desired alkene product from any of our intermediates, we wondered whether it would be possible to quench the carbon radical with a hydrogen atom donor (HAD) in place of the copper species, thereby generating an alkane product rather than an alkene.

From a screening of various HADs, we found that thiophenol gave the best results. After optimization of the other reaction parameters, we generated the desired fragmentation product **2′** in 80% isolated yield on a 10-g scale (Scheme 2). Because of known reproducibility issues when scaling up these types of reactions,[14d] we were pleased with the consistency obtained when performing the transformation on a 50-g scale—while simultaneously circumventing the need for column chromatography (purification through trituration diminished the yield slightly, to approximately 65%).

The fragmented mesylate **2′**, when subjected to alkylation and oxidation, generated the exo- and endo-P-phenyl phosphine oxides **3e** and **3e′** as a 2:1 mixture (Scheme 3). Reduction of these oxides proceeded in near-quantitative yields to give the free phosphines **4e** and **4e′**, which we screened for the allene–imine [3 + 2] annulation.

Similar to the behavior of our Hyp-derived chiral phosphines, the diastereomeric phosphines **4e** and **4e′** functioned as pseudoenantiomers for the annulation process (Table 3).[6,15] The catalyst **4e**, with an *S*-configuration at the phosphorus center, provided the adducts **7** with the (*S,S*)-configuration, while the catalyst **4e′**, with an *R*-configuration at the phosphorus center, provided the adducts **7′** with an (*R,R*)-configuration. For the reactions of the *γ-tert*-butylallenoate **5e**, both the phosphines **4e** and **4e′** gave high levels of ee (entries 1 and 2). In stark contrast to the 39% ee obtained for the pyrroline **7da** from the reaction mediated by the phosphine **4b** (see Table 2), the reactions catalyzed by the phosphines **4e** and **4e′** gave **7da** and its antipode **7da′** with ee's of 76 and 92%, respectively (entries 3 and 4). To modulate the nucleophilicity of the phosphorus center, we synthesized the *p*-anisyl phosphines **4f** and **4f′** and probed their annulation reactions. These catalysts gave better results (entries 5–8), with ee's ranging from 82–99%.

With our optimized catalyst design, we re-examined the scope of the allenoate and imine components in the allene–imine [3 + 2] annulations mediated by the endophosphine **4f′** (Table 4). Arylimines featuring electron-rich, electron-poor, mono-, di-, tri-, ortho-, meta-, and para-substituted phenyl and heteroaryl groups were all compatible with this catalyst and gave good results.[17] The *N*-sulfonyl protecting group was also interchangeable, permitting the use of *p*-tosyl, *p*-nosyl, and *p*-methoxyphenyl (PMP)-sulfonyl groups. Unlike the catalyst **4b**, which rendered high enantioselectivities only when reacting the *γ-tert*-butylallenoate **5e**, a wide range of substituents—including *γ-tert*-butyl (**7ei′**/**ej′**/**ek′**), *γ*-isopropyl (**7dj′**/**dl′**/**dm′**), *γ*-ethyl (**7ci′**/**cn′**/**co′**), *γ*-methyl (**7bh′**/**bm′**/**bp′**), *γ*-adamantyl (**7fa′**/ **fc′**), and *γ*-cyclohexyl (**7ga′**) groups—were tolerated in this **4f′**-mediated process, providing yields of 88–99% and ee's of 90–99%. Even the unsubstituted allenoate **5a** gave its products (**7aa′**/**al′**/**ap′**) in high yields (90–93%) and synthetically useful ee's (84–92%).

One product in Table 4 is particularly notable: the adduct **7aa′** formed from the reaction between the unsubstituted allenoate **5a** and *N*-tosylbenzaldimine (**6a**). Dubbed "efsevin," the pyrroline **7aa′** is a potent modulator of cardiac rhythmicity through regulation of mitochondrial Ca^{2+} uptake via the voltage-dependent anion channel 2 (VDAC2).[18a] It also displays prophylactic activity against ventricular tachycardia in a rodent model of human heart disease.[18b] Interestingly, neither of our pseudoenantiomeric Hyp-derived phosphines was capable of providing the efsevin eutomer; both the exo- and endo-P-phenyl phosphines **4g** and **4g′** produced (*S*)-efsevin (**7aa**). Because both enantiomers of carvone are readily available, it is possible to obtain the enantiomers of the catalysts **4e**/**4e′** and **4f**/**4f′**, thereby enabling the synthesis of either enantiomeric product. For example, the phosphine **4f′**, derived from (*R*)-carvone, delivered (*R*)-efsevin (**7aa′**) in 93% yield and 84% ee (Scheme 4). A single recrystallization enriched the ee to greater than 99%.

In summary, we have synthesized novel P-stereogenic chiral phosphines from the readily available (*R*)- and (*S*)-carvones and applied them to enantioselective [3 + 2] annulations of allenoates and imines to obtain a series of pyrrolines, including the biologically active molecule efsevin.[19] During the course of this study, we developed a new reaction enabling the one-pot formation of an alkane through fragmentation of an isopropenyl group. Further

efforts directed toward the application of this technology in the construction of pharmaceutically useful heterocyclic adducts will be outlined in due course.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

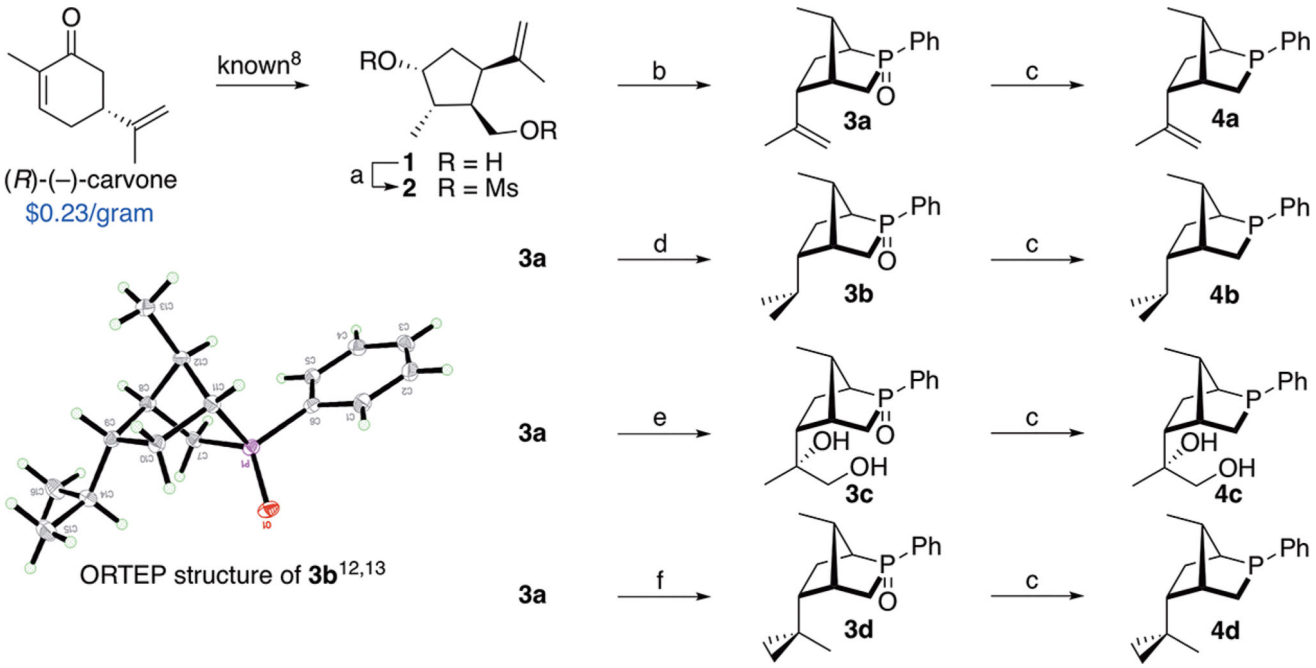
1. (a) Ojima I. Catalytic Asymmetric Synthesis. Wiley-VCH: Weinheim; 1999. (b) Noyori R. Asymmetric Catalysis in Organic Synthesis. John Wiley & Sons, Inc: New York; 1994. (c) Borner A. Phosphorus Ligands in Asymmetric Catalysis: Synthesis and Applications. Vol. 1–3. Wiley-VCH; Weinheim: 2008.
2. (a) Zhu G, Chen Z, Jiang Q, Xiao D, Cao P, Zhang X. Asymmetric [3 + 2] Cycloaddition of 2,3-Butadienoates with Electron-Deficient Olefins Catalyzed by Novel Chiral 2,5-Dialkyl-7-phenyl-7-phosphoabicyclo[2.2.1]heptanes. J. Am. Chem. Soc. 1997; 119:3836–3837.(b) Tang W, Zhang X. A Chiral 1,2-Bisphospholane Ligand with a Novel Structural Motif: Applications in Highly Enantioselective Rh-Catalyzed Hydrogenations. Angew. Chem., Int. Ed. 2002; 41:1612–1614.
3. (a) Vedejs E, Daugulis O. A Highly Enantioselective Phosphabicyclooctane Catalyst for the Kinetic Resolution of Benzylic Alcohols. J. Am. Chem. Soc. 2003; 125:4166–4173. [PubMed: 12670239] (b) Hoge G. Stereoselective Cyclization and Pyramidal Inversion Strategies for P-Chirogenic Phospholane Synthesis. J. Am. Chem. Soc. 2004; 126:9920–9921. [PubMed: 15303856]
4. Macaev FZ. Bioactive Natural Products from Enantiomeric Carvones. In: Atta-ur-Rahman Ed, editorStudies in Natural Products Chemistry. Vol. 39. Elsevier; Oxford: 2013.
5. (a) Fischer C, Defieber C, Suzuki T, Carreira EM. Readily Available [2.2.2]-Bicyclooctadienes as New Chiral Ligands for Ir(I): Catalytic, Kinetic Resolution of Allyl Carbonates. J. Am. Chem. Soc. 2004; 126:1628–1629. [PubMed: 14871082] (b) Defieber C, Paquin J-F, Serna S, Carreira EM. Chiral [2.2.2] Dienes as Ligands for Rh(I) in Conjugate Additions of Boronic Acids to a Wide Range of Acceptors. Org. Lett. 2004; 6:3873–3876. [PubMed: 15469371] (c) Gendrineau T, Chuzel O, Eijsberg H, Genet J-P, Darses S. C_1-Symmetric Monosubstituted Chiral Diene Ligands in Asymmetric Rhodium-Catalyzed 1,4-Addition Reactions. Angew. Chem., Int. Ed. 2008; 47:7669–7672.
6. Henry CE, Xu Q, Fan YC, Martin TJ, Belding L, Dudding T, Kwon O. Hydroxyproline-Derived Pseudoenantiomeric [2.2.1] Bicyclic Phosphines: Asymmetric Synthesis of (+)- and (−)-Pyrrolines. J. Am. Chem. Soc. 2014; 136:11890–11893. [PubMed: 25099350]
7. (a) Andrews IP, Kwon O. Enantioselective total synthesis of (+)-ibophyllidine via an asymmetric phosphine-catalyzed [3 + 2] annulation. Chem. Sci. 2012; 3:2510–2514. [PubMed: 22798981] (b) Gu Y, Hu P, Ni C, Tong X. Phosphine-Catalyzed Addition/Cycloaddition Domino Reactions of β'-Acetoxy Allenoate: Highly Stereoselective Access to 2-Oxabicyclo[3.3.1]nonane and Cyclopenta[a]pyrrolizine. J. Am. Chem. Soc. 2015; 137:6400–6406. [PubMed: 25905736] (c) Gao Z, Wang C, Yuan C, Zhou L, Xiao T, Guo H. Phosphine-catalyzed [4 + 1] annulation of 2-tosylaminochalcones with allenoates: synthesis of trans-2,3-disubstituted indolines. Chem. Commun. 2015; 51:12653–12656.(d) Cai L, Zhang K, Kwon O. Catalytic Asymmetric Total Synthesis of (−)-Actinophyllic Acid. J. Am. Chem. Soc. 2016; 138:3298–3301. [PubMed: 26910382] (e) Wu Y, Liu Y, Yang W, Liu H, Zhou L, Sun Z, Guo H. Chiral Phosphine-Catalyzed Enantioselective [3 + 2] Annulation of Morita-Baylis-Hillman Carbonates with Cyclic 1-Azadienes: Synthesis of Functionalized Cyclopentenes. Adv. Synth. Catal. 2016; 358:3517–3521.(f) Zhan G, Shi M-L, He Q, Lin W-J, Ouyang Q, Du W, Chen Y-C. Catalyst-Controlled Switch in Chemo- and Diastereoselectivities: Annulations of Morita-Baylis-Hillman Carbonates from Isatins. Angew. Chem., Int. Ed. 2016; 55:2147–2151.(g) Wang C, Gao Z, Zhou L, Yuan C, Sun Z, Xiao Y, Guo H. Phosphine-Catalyzed [2 + 4] Annulation of Allenoates with Thiazolone-Derived Alkenes: Synthesis

of Functionalized 6,7-Dihydro-5H-pyrano[2,3-d]thiazoles. Org. Lett. 2016; 18:3418–3421. [PubMed: 27378106] (h) Zhou L, Yuan C, Zhang C, Zhang L, Gao Z, Wang C, Liu H, Wu Y, Guo H. Enantioselective Synthesis of Quinazoline-Based Heterocycles through Phosphine-Catalyzed Asymmetric [3 + 3] Annulation of Morita-Baylis-Hillman Carbonates with Azomethine Imines. Adv. Synth. Catal. 2017; 359:2316–2321.(i) Zhang K, Cai L, Yang Z, Houk KN, Kwon O. Bridged [2.2.1] Bicyclic Phosphine Oxide Facilitates Catalytic γ-Umpolung Addition–Wittig Olefination. Chem. Sci. 2018; 9:1867–1872. [PubMed: 29732112]

8. (a) Pogrebnoi S, Saraber FCE, Jansen BJM, de Groot A. Synthesis of a chiral steroid ring D precursor starting from carvone. Tetrahedron. 2006; 62:1743–1748.(b) Andrews SP, Ball M, Wierschem F, Cleator E, Oliver S, Hogenauer K, Simic O, Antonello A, Hunger U, Smith MD, Ley SV. Total Synthesis of Five Thapsigargins: Guaianolide Natural Products Exhibiting Sub-Nanomolar SERCA Inhibition. Chem. - Eur. J. 2007; 13:5688–5712. [PubMed: 17508363] (c) Yang H, Gao Y, Qiao X, Xie L, Xu X. Concise Total Synthesis of (−)-8-Epigrosheimin. Org. Lett. 2011; 13:3670–3673. [PubMed: 21675754]
9. (a) Xu Z, Lu X. Phosphine-catalyzed [3 + 2] cycloaddition reaction of methyl 2,3-butadienoate and N-tosylimines. A novel approach to nitrogen heterocycles. Tetrahedron Lett. 1997; 38:3461–3464. (b) Zhu X-F, Henry CE, Kwon O. A highly diastereoselective synthesis of 3-carbethoxy-2,5-disubstituted-3-pyrrolines by phosphine catalysts. Tetrahedron. 2005; 61:6276–6282.(c) Zhao G-L, Shi M. Aza-Baylis-Hillman Reactions of N-Tosylated Aldimines with Activated Allenes and Alkynes in the Presence of Various Lewis Base Promoters. J. Org. Chem. 2005; 70:9975–9984. [PubMed: 16292830] (d) Ng PY, Masse CE, Shaw JT. Cycloaddition Reactions of Imines with 3-Thiosuccinic Anhydrides: Synthesis of the Tricyclic Core of Martinellic Acid. Org. Lett. 2006; 8:3999–4002. [PubMed: 16928058] (e) Fang Y-Q, Jacobsen EN. Cooperative, Highly Enantioselective Phosphinothiourea Catalysis of Imine–Allene [3 + 2] Cycloadditions. J. Am. Chem. Soc. 2008; 130:5660–5661. [PubMed: 18393504] (f) Han X, Zhong F, Wang Y, Lu Y. Versatile Enantioselective [3 + 2] Cyclization between Imines and Allenoates Catalyzed by Dipeptide-Based Phosphines. Angew. Chem., Int. Ed. 2012; 51:767–770.(g) Han X, Chan W-L, Yao W, Wang Y, Lu Y. Phosphine-Mediated Highly Enantioselective Spirocyclization with Ketimines as Substrates. Angew. Chem., Int. Ed. 2016; 55:6492–6496.
10. See the SI for details on reaction parameter optimization.
11. Please see the SI for the proposed transition state models and discussions of the factors governing stereoselection of these reactions.
12. The ORTEP structure is that of the (*S*)-carvone-derived **3b**.
13. CCDC 1814004 (**3b**) and CCDC 1814005 (**3c**) contain supplementary crystallographic data, which can be obtained free of charge from The Cambridge Crystallographic Data Centre.
14. (a) Schreiber SL. Fragmentation reactions of α-alkoxy hydroperoxides and application to the synthesis of the macrolide (+)-recifeiolide. J. Am. Chem. Soc. 1980; 102:6163–6165.(b) White JD, Grether UM, Lee C-S. (R)-(+)-3,4-DIMETHYLCYCLOHEX-2-EN-1-ONE. Org. Synth. 2005; 82:108.(c) Qi X-L, Zhang J-T, Feng J-P, Cao X-P. Total synthesis and absolute configuration of malyngamide W. Org. Biomol. Chem. 2011; 9:3817–3824. [PubMed: 21445440] (d) Huang D, Schuppe AW, Liang MZ, Newhouse TR. Scalable procedure for the fragmentation of hydroperoxides mediated by copper and iron tetrafluoroborate salts. Org. Biomol. Chem. 2016; 14:6197–6200. [PubMed: 27273761] (e) Liffert R, Linden A, Gademann K. Total Synthesis of the Sesquiterpenoid Periconianone A Based on a Postulated Biogenesis. J. Am. Chem. Soc. 2017; 139:16096–16099. [PubMed: 29076340]
15. See reference 6 for calculated transition state models.
16. When the reaction was run with 1.2 equivalents of the allenoate **5e** and 5, 10, and 15 mol% of the catalyst **4f′** the enantioselectivity remained at 99% ee with product yields of 77, 92, and 95%, respectively.
17. Our attempt to couple *N*-tosylpivaldimine with ethyl γ-tert-butyl- and γ-isopropylallenoate in the presence of the phosphine **4f′** did not result in any products, presumably because of the low electrophilicity of this alkylimine.
18. (a) Shimizu H, Schredelseker J, Huang J, Lu K, Naghdi S, Lu F, Franklin S, Fiji HDG, Wang K, Zhu H, Tian C, Lin B, Nakano H, Ehrlich A, Nakai J, Stieg AZ, Gimzewski JK, Nakano A, Goldhaber JI, Vondriska TM, Hajnoczky G, Kwon O, Chen J. Mitochondrial Ca^{2+} uptake by the

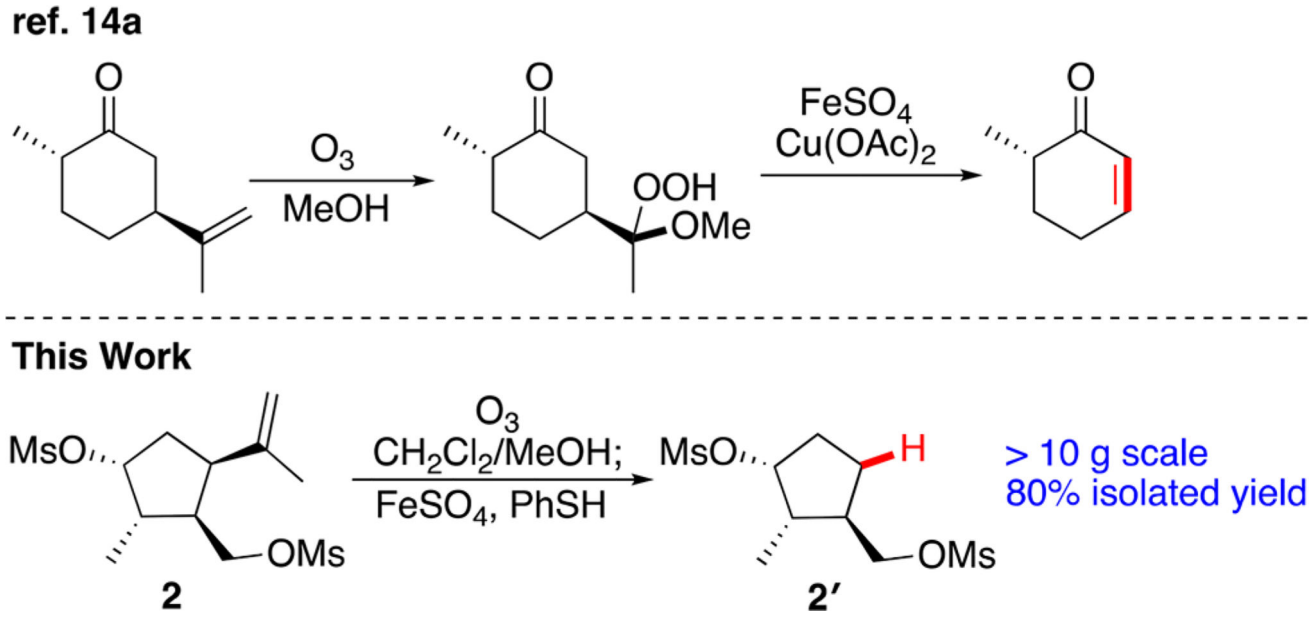
voltage-dependent anion channel 2 regulates cardiac rhythmicity. eLife. 2015; 4:e04801.(b) Schweitzer MK, Wilting F, Sedej S, Dreizehnter L, Dupper NJ, Tian Q, Moretti A, My I, Kwon O, Priori SG, Laugwitz K-L, Storch U, Lipp P, Breit A, Schnitzler MM, Gudermann T, Schredelseker J. Suppression of Arrhythmia by Enhancing Mitochondrial Ca^{2+} Uptake in Catecholaminergic Ventricular Tachycardia Models. JACC: Basic Transl. Sci. 2017; 2:737–747. [PubMed: 29354781]

19. In our laboratory, we refer to our hydroxyproline- and carvone-derived series of phosphines as HypPhos and CarvoPhos, respectively.

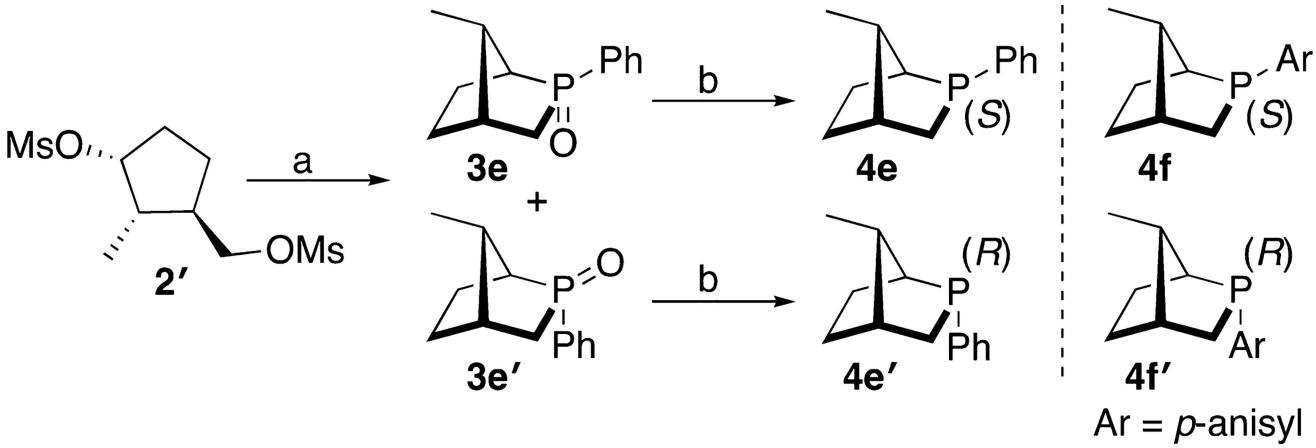


Scheme 1. Synthesis of Carvone-Derived Phosphines[†]

[†](a) MsCl, Et_3N (98%). (b) $PhPH_2$, *n*-BuLi; H_2O_2 (87%). (c) $HSiCl_3$ (**4a**: 95%; **4b**: 96%; **4c**: 91%; **4d**: 95%). (d) Wilkinson's catalyst, H_2 (91%). (e) AD-mix-α (94%). (f) Et_2Zn, CH_2I_2 (43%). For abbreviations and full experimental details, see the Supporting Information (SI).

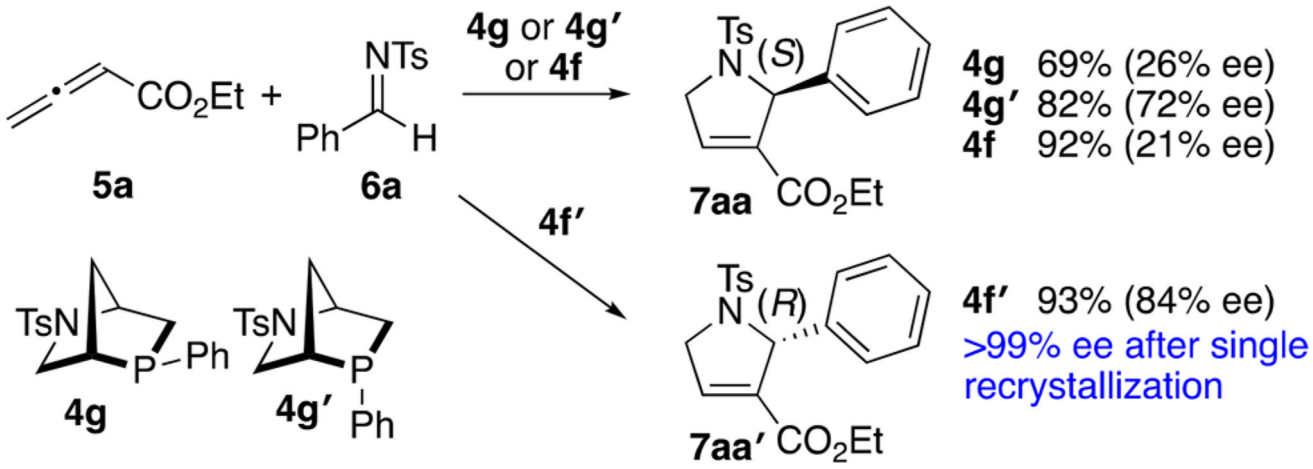


Scheme 2. Ozonolytic Fragmentation of the Mesylate 2



Scheme 3. Synthesis of the Phosphines 4e, 4e′, 4f, and 4f′[§]

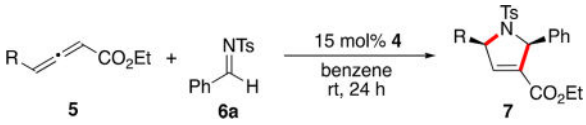
[§](a) $PhPH_2$, *n*-BuLi; H_2O_2 (2:1 exo/endo, 80% combined). (b) $HSiCl_3$, Et_3N (**4e**: 98%; **4e′**: 94%; **4f**: 98%; **4f′**: 99%). For abbreviations and full experimental details, see the SI.



Scheme 4. Synthesis of Efsevin Eutomer (7aa′)

Table 1

Enantioselective Allenoate–Imine [3 + 2] Annulations Catalyzed by the Phosphines 4a–d



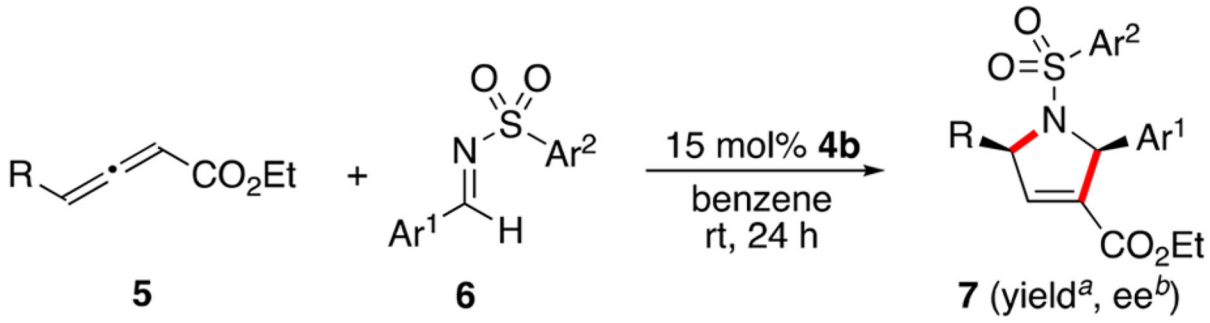
entry	cat.	5 (R)	yield (%)[a]	ee (%)[b]
1	4a	5a (H)	95 (7aa)	15
2	4a	5b (Me)	89 (7ba)	50
3	4a	5c (Et)	84 (7ca)	67
4	4a	5d (*i*Pr)	82 (7da)	38
5	4a	5e (*t*Bu)	95 (7ea)	82
6	4b	5e (*t*Bu)	94 (7ea)	93
7	4c	5e (*t*Bu)	91 (7ea)	77
8	4d	5e (*t*Bu)	NR	NR

[a] Isolated yield after column chromatography (SiO_2).

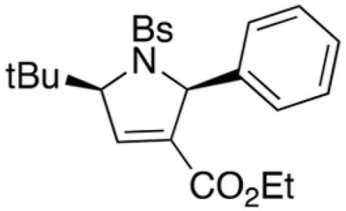
[b] Determined through HPLC [REGIS (*R,R*)-DACH DNB column]. For abbreviations and full experimental details, see the SI.

Table 2

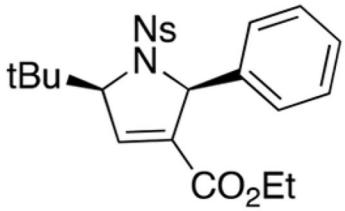
Enantioselective Allenoate–Imine Annulations Catalyzed by the Phosphine 4b



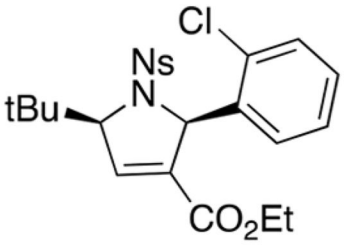
5 **6** **7** (yield[a], ee[b])



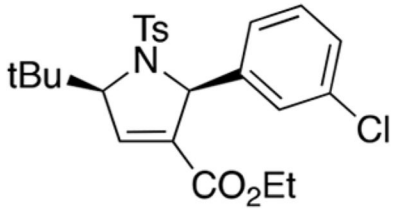
7eb (90%, 92% ee)



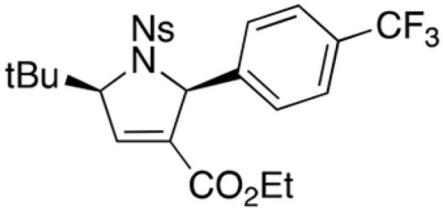
7ec (94%, 95% ee)



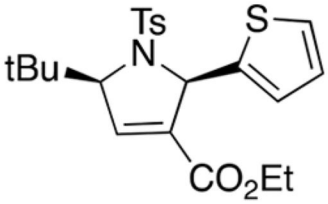
7ed (96%, 98% ee)



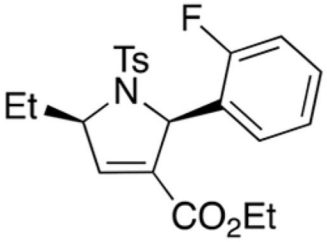
7ee (89%, 94% ee)



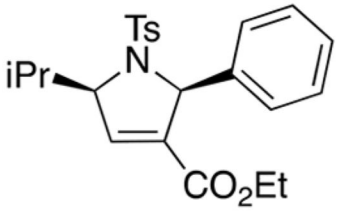
7ef (89%, 92% ee)



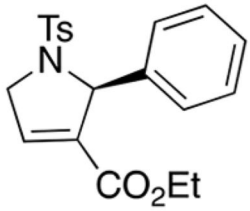
7eg (89%, 92% ee)



7ch (93%, 83% ee)



7da (84%, 39% ee)



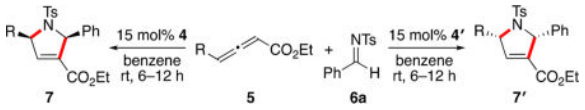
7aa (84%, 35% ee)

[a] Isolated yield after column chromatography (SiO_2).

[b] Determined through HPLC [REGIS (*R,R*)-DACH DNB column]. For abbreviations and full experimental details, see the SI.

Table 3

Enantioselective Allenoate–Imine Annulations Catalyzed by the Phosphines 4e, 4e′, 4f, and 4f′



entry	cat.	5 (R)	yield (%)[a]	ee (%)[b]
1	4e	5e (*t*Bu)	96 (7ea)	94
2	4e'	5e (*t*Bu)	98 (7ea')	−97
3	4e	5d (*i*Pr)	73 (7da)	76
4	4e'	5d (*i*Pr)	99 (7da')	−92
5	4f	5e (*t*Bu)	95 (7ea)	98
6[c]	4f'	5e (*t*Bu)	94 (7ea')	−99
7	4f	5d (*i*Pr)	96 (7da)	82
8	4f'	5d (*i*Pr)	97 (7da')	−94

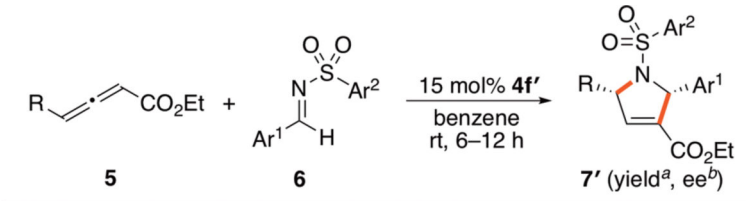
[a] Isolated yield after column chromatography (SiO_2).

[b] Determined through HPLC [REGIS (*R,R*)-DACH DNB column]. For abbreviations and full experimental details, see the SI.

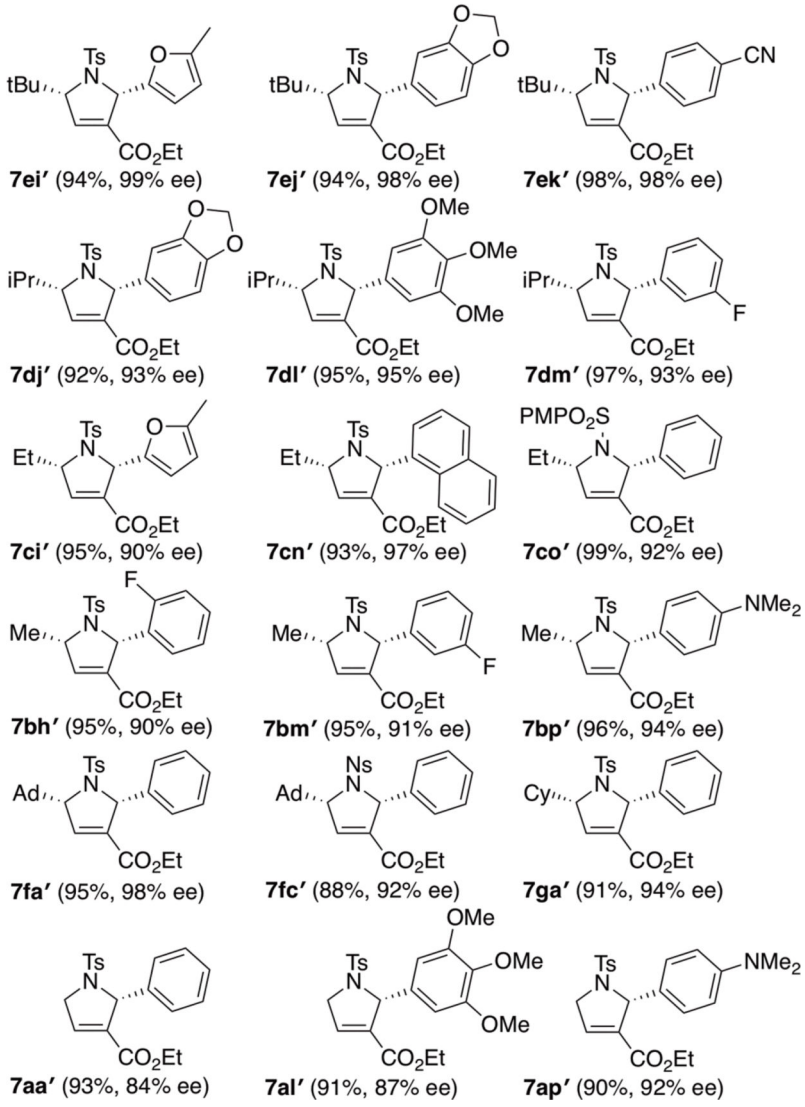
[c] See ref 16.

Table 4

Enantioselective Allenoate–Imine [3 + 2] Annulations Catalyzed by the Phosphine 4f′



5 6 7′ (yield[a], ee[b])



[a] Isolated yield after column chromatography (SiO_2).

[b] Determined through HPLC [REGIS (*R,R*)-DACH DNB column]. For abbreviations and full experimental details, see the SI.