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Enantioselective Decarboxylative Alkylation Reactions: Catalyst Development, Substrate Scope, and Mechanistic Studies

Dr. Douglas C. Behenna[‡], **Dr. Justin T. Mohr**[‡], **Dr. Nathaniel H. Sherden**, **Smaranda C. Marinescu**, **Andrew M. Harned[Prof.]**, **Dr. Kousuke Tani**, **Dr. Masaki Seto**, **Dr. Sandy Ma**, **Dr. Zoltán Novák**, **Dr. Michael R. Krout**, **Dr. Ryan M. McFadden**, **Dr. Jennifer L. Roizen**, **Dr. John A. Enquist Jr.**, **Dr. David E. White**, **Samantha R. Levine**, **Krastina V. Petrova**, **Dr. Akihiko Iwashita**, **Dr. Scott C. Virgil**, and **Brian M. Stoltz**[*] **[Prof.]**
The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 E. California Blvd., MC 101-20, Pasadena, CA 91125 (USA)

Abstract

α-Quaternary ketones are accessed through novel enantioselective alkylations of allyl and propargyl electrophiles by unstabilized prochiral enolate nucleophiles in the presence of palladium complexes with various phosphinooxazoline (PHOX) ligands. Excellent yields and high enantiomeric excesses are obtained from three classes of enolate precursors: enol carbonates, enol silanes, and racemic β-ketoesters. Each of these substrate classes functions with nearly identical efficiency in terms of yield and enantioselectivity. Catalyst discovery and development, the optimization of reaction conditions, the exploration of reaction scope, and applications in target-directed synthesis are reported. Experimental observations suggest that these alkylation reactions occur through an unusual inner-sphere mechanism involving binding of the prochiral enolate nucleophile directly to the palladium center.

Keywords

Asymmetric catalysis; Allylic alkylation; Enolates; Reaction Mechanism; Synthetic methods

Introduction

The catalytic asymmetric synthesis of all-carbon quaternary stereocenters stands as a significant challenge in synthetic chemistry.[1] Despite the demanding sterics of quaternary stereocenter formation, a number of useful catalytic transformations, including Diels–Alder,[2] Heck,[3] cyclopropanation,[4] alkylation,[5] acylation,[6] desymmetrization,[7] and pericyclic[8] reactions, among others, have been successful in generating these moieties. Although palladium-catalyzed enantioselective allylic alkylation chemistry has been an important tool for organic synthesis, only relatively recently has palladium(II) π-allyl chemistry been used for the formation of quaternary stereocenters.[9] The vast majority of palladium-catalyzed C–C bond forming allylic alkylations studied by Trost, Helmchen, Pfaltz, and others form tertiary stereocenters by the attack of stabilized (e.g., malonate) anions on prochiral 1,3-disubstituted allyl fragments.[9] Helmchen has shown that such reactions with palladium phosphinooxazoline (PHOX) complexes typically occur via an outer-sphere malonate attack at the allyl termini.[10] Although allylic alkylation mediated by

Fax: (+1)626-564-9297, stoltz@caltech.edu.
‡These authors contributed equally to this effort.

other metals, especially copper,[11] has successfully generated quaternary centers on prochiral allyl groups, to our knowledge this mode of reactivity has not been realized with palladium.[12]

An alternative, less common strategy in allylic alkylation is the use of prochiral nucleophiles. A quaternary stereocenter may be formed on a prochiral nucleophile when it possesses three distinct substituents. Such reactions require a remote chiral ligand to discriminate between the prochiral faces of an incoming nucleophile, and thus may seem a more challenging strategy. However, Hayashi,[13] Ito,[14] and Trost[15] have reported the asymmetric allylation of prochiral enolates derived from 1,3-dicarbonyl compounds. Trost and coworkers demonstrated that diamine-derived ligands **6** and **7**, which were designed to project bulk in front of the allyl fragment due to their large bite angle, are able to favor one face of the in situ generated ketone enolate (Scheme 1).[16],[17],[18] These reactions represented a significant advance in asymmetric allylation technology by forming quaternary stereocenters with excellent yield and good ee. However, the substrate scope of these reactions was restricted to ketone substrates containing either a single acidic site (e.g., ketone **1** and tetralone **2**) or two α-sites that have a large difference in acidity (e.g., β-ketoester **4** and α-phenyl ketone **5**).[1d] These limitations prevented direct access to fundamental α-quaternary ketones, such as 2-allyl-2-methylcyclohexanone (**9**), a cyclohexanone derivative not known as a single enantiomer prior to our work.[19]

We were confronted by these limitations during studies toward the synthesis of several natural products.[20] A survey of the literature revealed that the non-enantioselective alkylation reactions developed by Tsuji in the early 1980s had the proper reactivity and selectivity to form quaternary stereocenters in the presence of less substituted ketone α-sites of similar acidity. For example, allyl enol carbonate and allyl β-ketoester substrates contain both a latent enolate and allyl fragment (Scheme 2, A and B).[21] Alternatively, enol acetates and silyl enol ethers may serve as enolate precursors in intermolecular reactions with allyl carbonates (Scheme 2, C and D).[22] These alkylations have the advantage that the reaction occurs under nearly neutral conditions and often at mild temperatures. Despite their advantages, these alkylation reactions had been utilized rarely during the intervening twenty years between 1983 and the time we began research in 2003.[23],[24]

Our analysis of Tsuji's alkylation reaction showed it to be an ideal candidate for asymmetric catalysis. These high yielding alkylation methods are a clear case of ligand-accelerated catalysis, occurring only in the presence of phosphine ligands.[25] Of additional interest was the regiochemical fidelity observed in the alkylation reactions (Scheme 3). Tsuji demonstrated that both the tetrasubstituted allyl enol carbonate isomer **8** and the trisubstituted allyl enol carbonate isomer **11** undergo reaction to give allylated ketones **9** and **12** in ratios essentially unchanged from that of the substrates.[21a] These reactions were believed to proceed via oxidative addition of palladium to the allyl fragment followed by loss of CO_2 to give [palladium(II)(allyl)] complex **13** and enolate **14**. However, the details involving the recombination of the ion pair to give cyclohexanone **9** and a palladium(0) species were unclear at the time of Tsuji's original reports.[26] Coupled with the ability to purify the stable enolate precursors, we believed that the regiochemical fidelity afforded in the palladium-catalyzed reaction would provide direct access to enantioenriched α-quaternary ketones if a suitable chiral ligand could be found.[27]

Results and Discussion

Initial Screening of Chiral Ligands

Our initial goal was to show that a chiral ligand could transmit useful levels of asymmetric induction in the reaction while maintaining the important property of enolate regiochemical

fidelity found in the non-enantioselective system. We chose allyl enol carbonate **8** as a test substrate to evaluate the effect of various ligands (Table 1). Although allyl enol carbonates are less common than the other enolate precursors explored by Tsuji, they allowed us to add a single, achiral reagent to our catalyst system without extraneous initiators or counterions that might affect enantioselectivity, whereas silyl enol ether, enol acetate, and β-ketoester substrates did not. In accord with Tsuji's reports, we performed our initial trials in dioxane. Due to the prevalence of bis(phosphine) ligands in asymmetric catalysis, we began with several privileged bis(phosphine) ligands, but found that only Trost's ligand (**6**) gave significant ee. However, commercially available (*R*)-QUINAP (**15**), a chelating N/P-type ligand,[28] gave more uniform ee with other ethereal solvents (cf. entries 5 and 6 in dioxane and THF). Encouraged, we quickly found that the phosphinooxazoline (PHOX) class of N/P-type ligands also provided excellent reactivity and promising levels of enantioselectivity. The ready availability of numerous amino acid-derived PHOX ligands[29] allowed us to rapidly identify that bulkier aliphatic groups on the oxazoline provided higher levels of enantioinduction, with (*S*)-*t*Bu-PHOX (**19**) providing α-quaternary ketone (*S*)-**9** in 86% ee when dioxane was used as solvent. Additionally, we observed slightly higher ee in reactions with (*R*)-*i*Pr-PHOX (**17**) and (*S*)-*t*Bu-PHOX (**19**) when THF was used as solvent (83% and 88% ee, respectively).[30] Having attained satisfying levels of enantioselectivity and selectivity in forming ketone **9**, we began a more thorough investigation of reaction conditions.

Optimization of Reaction Parameters

The straightforward experimental procedure for asymmetric alkylation provided several opportunities to optimize the reaction. One important experimental parameter was found to be the complexation time for (*S*)-*t*Bu-PHOX (**19**) and tris(dibenzylideneacetone)dipalladium(0) ($Pd_2(dba)_3$) prior to addition of the substrate.[31] Mixing the metal and ligand for 30 min before substrate addition resulted in a balance between short complexation times (e.g., 5 min) in which lower yields but complete consumption of the substrate were observed, and longer complexation times (e.g., 1–3 h) in which poor conversion was observed. Storing the catalyst–metal complex for an extended time seemed to be complicated by the introduction of adventitious amounts of O_2 that readily oxidized the ligated PHOX molecule at phosphorus, thereby preventing significant consumption of the starting material.[32]

We also investigated the effect of concentration on the reaction (Table 2). At higher concentrations, significantly lower yields were observed, as well as slightly decreased ee. No further increase in enantioselectivity was observed below 0.03 M.

Encouraged by our initial discovery that reactions in THF gave better levels of enantioinduction than those in dioxane, we undertook a more thorough study of solvent effects on the reaction (Table 3). Many of the ethereal solvents investigated gave good results. Diethyl ether, *tert*-butyl methyl ether (TBME), and diisopropyl ether all provided good yields and slightly higher ee than reactions in THF with allyl enol carbonate **8** (entries 3–5). However, the methyl tetralone-derived allyl enol carbonate **20** yielded products with substantially lower ee in diethyl ether and TBME. The poor solubility of the catalyst in these less coordinating ethereal solvents occasionally led to incomplete conversion, a disadvantage that outweighed the slight increase in ee. Interestingly, several non-ethereal solvents also performed well in the transformation. Reactions in benzene and toluene gave similar yield and enantioinduction as those in THF (entries 8 and 9). The reaction tolerated carbonyl-containing solvents: ethyl acetate (entry 10) provided good yields and enantioselectivity in the asymmetric allylation, although acetone (entry 11) afforded inferior yield and ee. Interestingly, triethylamine produced a level of enantioselectivity equal to that

observed with the best ethereal solvents, albeit with lower yield (entry 12). Halogenated solvents fared poorly in the reaction, suffering from low conversion and yield (entries 13–15). Overall, we were intrigued by the variety of solvents with vastly different properties that performed equally well.

Fine Tuning of Phosphinooxazoline Ligands

A substantial effort was undertaken to improve the enantioselectivity of the reaction by modifying the PHOX ligand structure (Table 4).[33] Hoping to continue the trend of increasing enantioselectivity initially noted in moving from *i*Pr- to *t*Bu-PHOX (entries 2 and 4), we undertook the synthesis of numerous PHOX ligands with varied sterics and evaluated these ligands in the reaction of allyl enol carbonates **8** and **20**. In general, ligands bearing saturated substituents on the oxazoline fragment performed better than those with aryl groups in terms of ee. Moving the steric bulk away from the oxazoline framework by inserting a methylene group (i.e., ligand **23**, entry 6) substantially lowered enantioselectivity. Of particular note are the L-serine-derived ligands **27** and **28** (entries 10 and 11),[34] which allowed access to the enantiomeric *R* product series with nearly the same level of enantioselectivity as that observed with (*S*)-*t*Bu-PHOX (**19**), but without the need for more costly (*R*)-*tert*-leucine.[35] The known *cis*-1-amino-indan-2-ol-derived ligand **29** and borneol-derived ligand **30**, both with uniquely shaped substituents, gave slightly lower enantioselectivity relative to *t*Bu-PHOX (**19**).[36] It is noteworthy that regardless of the shape or type of the substituent on the PHOX ligand, the ketone products contained quaternary stereocenters with a consistent sense of configuration (e.g., (*S*)-PHOX ligands provide (*S*)-**9**).[37] With *t*Bu-PHOX (**19**) established as the optimal steric framework, we next considered the electronics of the ligand.[38]

A number of *t*Bu-PHOX derivatives were synthesized to probe the importance of phosphine electronics (Table 5). We investigated ligands ranging from electron rich to electron poor phosphines with allyl enol carbonates **20** and **8** (entries 1–7 and 8–14, respectively). The electronic perturbation had no significant effect on reaction yield, but ligands bearing electron withdrawing groups (especially CF_3 groups) gave a significant increase in the *rate* of reaction with allyl enol carbonate substrates.[33a] Further, electron releasing *para* substituents on the phenyl rings tended to lower the ee of the product relative to that observed with (*S*)-*t*Bu-PHOX (entries 1 and 8). When tetralone-derived allyl enol carbonate **20** was used as the substrate, a slight increase in enantioselectivity was observed with electron withdrawing substitution at the *p*-phenyl positions (entries 3–5). However, enantioselectivity decreased significantly with extremely electron poor PHOX ligands (entries 6 and 7). This trend was not apparent in the enantioselectivity with cyclohexyl-derived allyl enol carbonate **8** (entries 8–14). These results suggest a subtle interplay between ligand and substrate electronics.

As a final perturbation of the PHOX ligand structure, we prepared a number of non-N/P mixed chelates based on the phenyl oxazoline skeleton of the PHOX ligands (Table 6).[39] The phosphine oxide of *t*Bu-PHOX is inactive as a catalyst.[32] A sulfur analogue also failed to catalyze the reaction (Table 6, entry 1).[40] Moving down the periodic table from phosphorus, the arsenic analogue of *t*Bu-PHOX had excellent activity as a catalyst, but gave tetralone **3** in only moderate ee (entry 2). A nitrogen analogue showed little catalytic activity, and the small amount of product generated was nearly racemic (entry 3). As a final derivative that maintains the six-membered chelation, but changes the hybridization of the backbone atoms involved, a known phosphinite ligand, SimplePHOX, was found to give only moderate ee (entry 4).[41]

Although some electron deficient derivatives of *t*Bu-PHOX did provide slightly better product ee with certain substrates, ultimately this slight improvement did not typically offset the added difficulty in synthesizing substituted PHOX ligands.[33] Our studies clearly showed that N/P chelates were particularly effective at inducing high levels of asymmetry in the allylation. As a result, we retained the use of (S)-*t*Bu-PHOX (**19**) in our optimized conditions for exploring the scope of the reaction.

Asymmetric Allylation of Allyl Enol Carbonates

We have successfully employed a variety of allyl enol carbonates in our asymmetric Tsuji allylation (Table 7).[42] The allyl group may be substituted at the internal position resulting in slightly higher levels of asymmetric induction (entry 4). The cyclic portion may be unsaturated (entry 5), substituted (entries 6–11), appended (entries 12 and 13), or enlarged (entries 14 and 15). Among these variations, several are particularly noteworthy: the presence of a conjugate acceptor enone (entry 5) does not lead to Michael addition products, highlighting the essentially neutral reaction conditions; quaternary stereocenters may be synthesized vicinal to pre-existing fully substituted carbons (entry 8); the temperature may be lowered in order to improve enantioselectivity when highly reactive substrates are employed (entries 12 and 13), although the reaction time increases significantly.[43] Overall, we were pleased to find that a wide range of functionalized enantioenriched cycloalkanones were accessible by this method.

Our use of allyl enol carbonates enabled direct access to α-quaternary ketones with multiple acidic sites. However, allyl enol carbonates are rarely encountered in the literature, and the synthesis of isomerically pure enol carbonates[44] often required the synthesis of silyl enol ethers as intermediates. Since Tsuji had used silyl enol ethers in his non-enantioselective allylation, we contemplated adapting our conditions such that silyl enol ethers could be employed directly.

Asymmetric Allylation of Silyl Enol Ethers

Silyl enol ethers are commonly encountered enolate equivalents. Unlike allyl enol carbonates, silyl enol ethers render the alkylation reaction intermolecular, with the enolate precursor and allyl fragment introduced separately. We discovered in our initial studies that silyl enol ethers were not sufficiently nucleophilic to react with the [Pd(II)(allyl)] fragment under our reaction conditions at 25 °C. However, we found that the reaction could be initiated in the presence of tetra-*n*-butylammonium difluorotriphenylsilicate (TBAT), a commercially available dry fluoride source.

The use of TBAT as an initiator complicated the proposed catalytic cycle (Scheme 4). In the case of allyl enol carbonates, the oxidative addition of allyl carbonate **8** and rapid decarboxylation led directly to the enolate/[Pd(II)(allyl)] ion pair, which could collapse directly to the product (Scheme 3). For the intermolecular reaction, we primarily used diallyl carbonates as allyl precursors, although mixed carbonates were also effective. Oxidative addition of allyl carbonates occurs readily at 25 °C to give [Pd(II)(allyl)] species **13**, CO_2, and an alkoxide. The addition of TBAT immediately generates the enolate, which could react with palladium complex **13** by the same enantioselective mechanism observed with allyl enol carbonates. A substoichiometric amount of TBAT was sufficient, as the alkoxide formed in the reaction is also capable of providing the enolate in situ. In principle, it should be possible for the small amount of allyl alkoxide generated from oxidative addition to initiate the reaction.[45] In practice, we found that 35 mol% TBAT was usually sufficient to ensure complete conversion of the silyl enol ether (**40**). Having developed an effective means of silyl enol ether activation, we attempted asymmetric alkylation with a range of tetrasubstituted silyl enol ethers.

Gratifyingly, alkylation of the silyl enol ether substrates occurred with levels of enantioinduction similar to those observed for the allyl enol carbonate substrates and over a similar range of substrates (Table 8). Specifically, methyl- and ethyl-substituted quaternary ketones were produced with the same ee observed in the allyl enol carbonate reactions (entries 1 and 2). Tertiary ether stereocenters were accessible from an α-oxygenated silyl enol ether, albeit with moderate ee (entry 3). In addition to diallyl carbonate, dimethallyl carbonate served as a suitable allyl fragment precursor (entries 4 and 5). Interestingly, 2-allyl-2-methallylcyclohexanone, bearing only a remote methyl group to engender chirality, formed in 91% ee. As with the reactions of allyl enol carbonates, substitution about the ring and larger ring sizes were tolerated as well (entries 6–8).

In addition to the flexibility afforded by the intermolecular reaction of silyl enol ethers and diallyl carbonates, the use of silyl enol ethers as a means to generate enolates independent of the allyl fragment allowed the catalytic cycle to commence at the stage of a [Pd(II)(allyl)] complex **41** (Scheme 5). Upon mixing (*S*)-*t*Bu-PHOX, $[Pd(allyl)Cl]_2$, and NH_4PF_6 in ethanol,[46] $[Pd(II)(allyl)PHOX]^+[PF_6]^-$ salt **41** readily precipitated and this solid could be recrystallized and characterized crystallographically as a partial EtOH adduct.[47] The complex (**41**) serves as an active catalyst in the enol silane variant of our enantioselective alkylation reaction, giving good yield and nearly identical product ee compared to that observed with the in situ-generated catalyst. The $Pd(II)PF_6$ salt **41** has several practical advantages: it is an air stable, nonhygroscopic solid that may be stored indefinitely. Moreover, using the preformed [Pd(allyl)PHOX] catalyst obviated the introduction of dibenzylideneacetone (dba), which often complicated the purification of the α-quaternary ketone products.[48]

Enantioselective Alkylation of Dioxanone Substrates for the Synthesis of Tertiary Ethers and Alcohols

Given our success in preparing α-quaternary cycloalkanones, we wished to explore the direct synthesis of enantioenriched α-oxygenated ketones, which are a particularly challenging structure and appear in a number of biologically active compounds.[49] Our preliminary entries into these systems included a Baeyer–Villiger oxidation of an α-quaternary ketone (Scheme 9a, vide infra) and a single example of an oxygenated enol silane that provided a tertiary ether in only moderate ee (Table 8, entry 3). The latter result indicated that an exocyclic heteroatom directly attached to the putative enolate intermediate caused significant disruption to the stereocontrol elements of the catalyst. Therefore, we chose to explore a class of substrates with the heteroatom contained within the ring where it would be less likely to interact with the metal center.[27c] Dioxanone substrates have been employed in chiral auxiliary-controlled enolate alkylations, and we hypothesized that our catalytic enolate alkylation procedure might provide a more efficient entry into these oxygenated products.[50],[51]

We prepared enol silane **42** (Table 9) as a representative substrate of the dioxanone class.[52] We found that solvent had a relatively larger effect on the yield and ee of the product with this class of substrates (Table 9) and that a full equivalent of TBAT was required for efficient conversion of the TES enol ethers to product. In the optimal case, exposure of enol ether **42** to the complex derived from $[Pd(dmdba)_2]$[48] and (*S*)-**19**, diallyl carbonate, and TBAT (1 equiv) in toluene at 25 °C led to dioxanone product **43** in 74% yield and 88% ee. We explored the scope of this transformation and found that substitutions at the 2-position and on the allyl group were possible while maintaining high yields and product ee (Table 10). These oxygenated products were amenable to a number of subsequent transformations that enabled the enantioselective synthesis of several challenging structural motifs (Scheme 9d, vide infra).

Our work with silyl enol ethers demonstrated that our enantioselective process is robust enough to permit introduction of the enolate and allyl fragments separately and to tolerate the presence of other ions in solution. Silyl enol ethers are a more familiar substrate class and greatly increase the practicality of the reaction. However, we rely on thermodynamically driven silyl enol ether syntheses, which typically produce a 10:1 ratio of isomers that requires a somewhat tedious purification to obtain isomerically pure substrates.[44] A direct method for the synthesis of isomerically pure substrates would further increase the practicality of the catalyst system.[26] Nonetheless, the enantioselective alkylation reactions employing either allyl enol carbonate or enol silane substrates provide broad access to enantioenriched α-quaternary cycloalkanones.

Asymmetric Decarboxylative Allylation of β-Ketoesters

Encouraged by our previous results, we sought to exploit this technology for the preparation of a variety of interesting synthetic targets. In one such effort, we encountered difficulty in the preparation of the requisite enol carbonate or silyl enol ether (Scheme 6). A variety of conditions for enolate formation and trapping led to inseparable mixtures of enol isomers. As a consequence of the high degree of regiochemical fidelity in the allylation reaction,[21,22] corresponding mixtures of allylated products were obtained. To address this problem, we sought a different class of substrates for our catalytic reaction that would rely on an alternative method of enolate generation that was A) specific for the production of a desired tetrasubstituted enolate, B) did not rely on a thermodynamic equilibration under basic conditions, and C) maintained high enantioselectivity in the overall transformation.

Results and Discussion

Enantioselective Alkylation with Racemic Allyl β-Ketoesters

β-Ketoesters represent a classical solution to the problem of regioselective ketone alkylation (e.g., the acetoacetic ester synthesis).[54] In 1980, Tsuji and Saegusa reported allyl β-ketoesters as substrates in non-enantioselective Pd-catalyzed enolate alkylations.[21] We reasoned that an allyl β-ketoester might solve the problem of selective enolate formation in the course of an enantioselective allylation reaction. However, as stereogenic racemic substrates for a catalytic asymmetric reaction, allyl β-ketoesters presented some unique challenges: the catalyst must deallylate the substrate *nonselectively* to avoid kinetic resolution of the substrate, the C–C bond must break at a reasonable temperature in the decarboxylation step to prevent loss of selectivity in the subsequent bond-forming step, and the stereogenic intermediates must not experience diastereomeric transition states that are detrimental to the selectivity of the process.[55] Nonetheless, we prepared the appropriate substrate (**44**, Scheme 7) using standard methods[53] and exposed racemate (±)-**44** to our standard reaction conditions ($Pd_2(dba)_3$, (*S*)-*t*Bu-PHOX, THF, 25 °C). Unfortunately, no conversion was observed (by TLC) under these conditions after 24 h. However, we were delighted to find that elevating the temperature to 30 °C and carrying out the reaction in Et_2O restored reactivity, providing enone (−)-**45** in 73% yield (>99% conversion) and 86% ee after 9 h. This experiment provided a key proof-of-concept for an enantioconvergent reaction using a racemic allyl β-ketoester.

When further exploring this pivotal reaction, we noted that no significant kinetic resolution of the allyl β-ketoesters was observed.[56] In fact, this facet of the reaction was critical in order to obtain high yield in a reasonable reaction time. The similar levels of enantioselectivity observed with the allyl β-ketoester substrates and the other substrate classes (cf. Tables 7 and 8 with Tables 12 and 13) suggest that the enantiodetermining transition state of the reaction remains unchanged. Although the extent to which decarboxylation slowed at ambient temperature varied from substrate to substrate, β-

ketoesters were uniformly more sluggish in decarboxylation than allyl enol carbonates.[57] However, the rate of reaction increased greatly at slightly higher temperatures, and thus reasonable reaction times (~2 h) could be achieved by increasing the reaction temperature by ca. 5 °C, which had a negligible effect on product ee (Table 11).

This enantioconvergent reaction is unusual due to the use of quaternary β-ketoesters (Scheme 8). Typical stereomutative enantioconvergent processes (e.g., dynamic kinetic resolution) involve a pre-equilibrium epimerization of the starting material, **A**, followed by enantioselective conversion to product **B** (Pathway I).[58] However, quaternary stereocenters are not typically epimerizable, and we believe that both enantiomers of the starting material, **A**, convert irreversibly to a prochiral intermediate, **C**,[59] which preferentially forms one enantiomer of the product, **B**, under the influence of the chiral catalyst (Pathway II). We have termed such transformations as *stereoablative* enantioconvergent processes due to a lack of an existing term to adequately describe this interesting reaction pathway.[60],[61]

As a result of the facile synthesis of racemic quaternary β-ketoester substrates, we have been able to expand the substrate scope of the asymmetric alkylation greatly.[53] A number of α-substituted 2-carboxyallylcyclohexanones were readily prepared by the above methods and successfully underwent enantioconvergent decarboxylative allylation (Table 12). The system was permissive of an array of functionality and substitution, and formed products in excellent yield and high ee. Remarkably, the presumed enolate intermediate tolerated both enolizable (entries 4 and 5) and β-heteroatom (entry 9) substituents without side products corresponding to enolate scrambling or β-elimination.[62] Our conditions also allowed for incorporation of a fluorine atom for the high-yielding synthesis of a stereodefined tertiary fluoride (entry 10). Subsequent to our initial disclosure, others have utilized this chemistry to prepare a range of tertiary fluoride-containing compounds that could be of interest as non-epimerizable pharmaceutical analogues.[42c],[42e],[42h],[42j],[63]

In addition to modifications at the α-position of the substrate, the decarboxylative asymmetric allylation of β-ketoesters was also amenable to a wide variety of modification to the carbocycle and allyl fragment (Table 13). In particular, the reaction was exceptionally tolerant to the steric demands of substitution at the 3-, 4-, 5-, and 6-positions of the cyclohexane ring; each position can be fully substituted without significantly affecting yield or enantioselectivity (entries 1–4). Important to multi-step synthetic efforts, we found the protocol to be scalable with no detriment to the results (entry 2).[64] Unsaturated substrates (entries 5 and 6) as well as seven-membered ring containing substrates (entries 7 and 8) performed well in the reaction. As with the previous substrate classes (i.e., allyl enol carbonates and silyl enol ethers), substitution at the central position of the allyl fragment had a beneficial effect on the enantioselectivity of the reaction (entries 9–11).[65] The incorporation of a chlorine atom on the allyl fragment (entry 10) provides both another functional group handle for further manipulation and a higher oxidation state. Inclusion of a phenyl group on the allyl fragment (entry 11) produced the highest ee product we have observed to date (94% ee). Heterocyclic compounds were also accessible by this method (entry 12). Vinylogous esters were competent in the reaction, but elevated temperatures (up to 80 °C) were required in some cases to achieve high conversion and the ee was somewhat decreased (entry 13). Employing a vinylogous thioester lowered the required temperature and permitted the isolation of highly enantioenriched product (entry 14).[66] This particular vinylogous thioester was employed in the enantioselective syntheses of (+)-carissone[24e] and (+)-cassiol[24f] (see Scheme 10e). We have demonstrated that dioxanones are viable substrates as well (entries 14 and 15). The tetrasubstituted α-alkoxycarbonyl products were furnished in good yields and enantiomeric excesses, and the products could be readily derivatized to access a number of enantioenriched α-hydroxycarbonyl compounds.[27c]

Challenging Substrate Classes

Synthesis of Tertiary Stereocenters from Acyclic Enolate Precursors—

Although we have principally employed our asymmetric allylation for the synthesis of fully-substituted stereocenters, the mild and nearly neutral conditions of the reaction are well suited for the synthesis of tertiary stereocenters α to carbonyls (Table 14).[67] Such stereocenters are prone to epimerization and over-alkylation under the strongly basic conditions traditionally used for enolate generation.[68] We found that the allyl enol carbonate underwent allylation to form phenyl ketone (*R*)-**46** in 67% ee (entry 1). In analogy to the results of Hou and coworkers,[18b] we found that the addition of AgBr gave a significant increase in the ee of the product (entry 2). Both TMS[69] and TBS[70] silyl enol ethers were competent enolate precursors when TBAT was used as an initiator (entries 3 and 4). Unlike the tetrasubstituted silyl enol ethers, CsF proved to be the optimal fluoride source for the less substituted silyl enol ethers, resulting in noticeably higher ee (entry 5). Unfortunately, the use of AgBr in the presence of CsF greatly reduced reactivity and only increased the product ee slightly (entry 6). Similarly, the use of ethyl ether as a solvent increased enantioselectivity at the expense of yield (entry 7). Although our allylation methods have provided tertiary stereocenters in only moderate ee, we have recently disclosed a complementary decarboxylative protonation of quaternary allyl β-ketoesters based on a similar catalyst system that provides access to tertiary stereocenters α to ketones in excellent ee.[71]

Application of the Palladium•PHOX Catalyst System to Propargylation—

In addition to allylation, we also explored propargylation of enol carbonates with the Pd•PHOX catalyst system (Table 15).[72] Our preliminary studies showed that propargylation of enol carbonate **47** required significantly higher temperatures than are needed for allylation.[73] Additionally, the optimal structure of the PHOX ligand is significantly different for propargylation than for allylation. Moving the bulk of the *t*Bu group away from the oxazoline by insertion of a methylene group gave (*S*)-**48** with higher ee (entries 1 and 2). Unlike allylation (cf. Table 4), PHOX ligands prepared from phenylalanine derivatives gave higher product ee than those prepared from saturated amino acids, with the 9-anthracenylalanine derivative (**51**) giving the highest level of enantioselectivity (entry 7, Table 15). Although still preliminary, these studies suggest that the Pd•PHOX catalyst system may find use with electrophiles other allyl groups.[27e],[71]

Substrates Proceeding via Weakly Basic Enolates—

The alkylation of substrates derived from ketones of unusually low pK_a (i.e., stabilized enolates) as a group gave by far the lowest levels of enantioselectivity we have observed with the Pd•PHOX catalyst system (Table 16). Despite the low selectivity, these substrates gave consistently excellent chemical yields of the allylated products. It is noteworthy that the β-ketoester (entries 1 and 2) and α-aryl ketone (entries 3 and 4) derived enolates, which gave excellent enantioselectivity in Trost's earlier asymmetric allylation reaction[15],[16b] failed to give useful levels of enantioinduction under our conditions.[74] An oxazole substrate, designed with the intention of executing an enantioselective synthesis of α,α-disubstituted amino acids, also underwent allylation with little enantioselectivity, presumably due to the stability of the intermediate aromatic enolate (entry 5). The orthogonality of the substrate scope, in terms of asymmetric induction, between our method and Trost's early reports may be indicative of fundamentally different mechanisms underlying the two allylation reactions and is an important piece of evidence in our mechanistic hypothesis.[26],[75]

Substrates Containing Five-Membered Rings—

Although enolate precursors contained in six-membered rings composed the bulk of our substrates, we have demonstrated that seven- and eight-membered rings are tolerated with only a slight decrease

in product ee (see Tables 7, 8, and 13). Allyl β-ketoesters constructed on five-membered rings provided modest to useful levels of enantioselectivity (Table 17). These substrates generally produced α-quaternary ketone products in good yields with enantiomeric excesses about 10% lower than that observed with the cyclohexanone analogue. Ethyl substituted cyclopentanone was formed in 86% ee, only 6% lower than observed with the corresponding cyclohexanone (entry 1). Indanones were produced in good yield and with useful ee (entries 4 and 5). Benzyl appended cyclopentanone substrates gave consistent yields, but electron deficient aromatic rings decreased product ee more significantly than in the reactions of six-membered β-ketoesters (entries 6–8).

Synthetic Applications

The α-quaternary cycloalkanones produced in the asymmetric Tsuji alkylation are highly useful chiral building blocks. Each substrate contains at least two functional groups, a ketone and an olefin, for further manipulation. Moreover, the preceding section has demonstrated these allylation reactions to be highly functional group tolerant. The application of this suite of allylation reactions to the catalytic asymmetric synthesis of natural products is an ongoing topic of research in our laboratories.[24]

To further demonstrate the utility of these products, we transformed ketone (*S*)-**9** into several familiar cyclic frameworks (Scheme 9a). Wacker oxidation of (*S*)-**9** followed by aldol condensation gave enone **52** in good yield. Another functionalized [6-5] skeleton was formed in a three-step sequence by olefin cross metathesis with methyl vinyl ketone catalyzed by Grubbs' second generation Ru-complex **53**,[76] olefin hydrogenation, and aldol condensation under basic conditions to afford exocyclic enone **54**. Carbocyclic [6-6] ring systems were accessible as well: multi-step elaboration of the allyl group afforded an intermediate diketone, which underwent aldol condensation to enone **55** in 42% overall yield. Enone **55**, which has been classically produced by Robinson annulation, has been used extensively in synthesis.[77] As a final transformation of (*S*)-**9**, we executed a Baeyer–Villiger oxidation with peracetic acid to give caprolactone **56**. This transformation demonstrates the conversion of our enantioenriched quaternary stereocenter into a latent tertiary alcohol with defined absolute stereochemistry and entry into acyclic systems.

Carbocyclic spiro compounds represent a particularly challenging subclass of quaternary stereocenters. To complement the syntheses of fused cyclic skeletons above, allyl methallyl ketone **57** was used as an entry into the synthesis of ring systems containing spiro quaternary stereocenters. Ketone **57** could be treated with Grubbs' second generation catalyst (**53**)[76] in dichloromethane to give a good yield of the spiro[4.5]ketone **58** (Scheme 9b). Spiro[5.5]enone **59** was produced in modest yield by treatment of ketone **57** with standard ketal protection conditions, followed by ozonolysis, and exposure to base (Scheme 9c).

The dioxanone class of substrates provided entries into other important derivatives (Scheme 9d). Cleavage of the acetal with *p*-toluenesulfonic acid generated dihydroxy ketones (e.g., **60** → **61**). These dihydroxy ketones underwent selective oxidative cleavage upon exposure to periodic acid and after esterification the corresponding hydroxyesters were isolated (e.g., **62**). Overall yields for the transformation from dioxanone to hydroxyester (**60** → **62**) were 41–81% for three steps. In the case of chlorinated compound **62**, subsequent ozonolysis formed citramalic acid dimethyl ester (**63**) that was correlated to literature data to establish the absolute configuration of dioxanone (−)-**60** as *S*.[78]

Similar tactics have enabled the use of the enantioselective Tsuji alkylation in a number of synthetic efforts.[24] Ketone (*S*)-**64** (Scheme 10a) was readily converted to enone **65**, which could be recrystallized via the semicarbazone derivative to 97% ee. Enantioenriched enone **65** was then elaborated to the antipode of the natural product dichroanone (**66**) in seven

additional steps.[24a] A strategy comprising enantioselective allylation and ring-closing metathesis was employed to synthesize the spirocyclic natural products laurencenone B (**68**) and elatol (**69**) from vinylogous ester **67** (Scheme 10b).[24c] An ongoing effort toward the preparation of the marine alkaloid zoanthenol (**72**) features α-quaternary ketone **70** as a key synthon for the preparation of the ABC tricyclic substructure (**71**) of the target molecule (Scheme 10c).[24b] Dioxanone **73** was converted to cyclohexene **74** in three steps and 50% yield (Scheme 10d). Hydroxy acid **74** has previously been employed in the synthesis of quinic acid (**75**),[79] a common chiral pool starting material used in many synthetic efforts,[80] including the total synthesis of dragmacidin F reported by our laboratory.[81] Vinylogous ester **76** is a versatile precursor and can be elaborated to the natural products carissone (**77**)[24e] and cassiol (**78**).[24f]

In an effort to construct more than one quaternary stereocenter in a single transformation, we designed substrate **79** (Scheme 11a), which contained a latent allyl β-ketoester moiety to be revealed by the reaction of the allyl enol carbonate portion of the molecule. To our delight, cascade allylation occurred to afford C_2-symmetric ketone **80** as the predominant product in 92% ee with 4:1 dr. Similarly, bis(β-ketoester) substrates may be employed in a stereoconvergent process where each of the three stereoisomeric starting materials (i.e., two C_2 symmetric enantiomers and one meso diastereomer) are converted to enantioenriched products with excellent stereocontrol (e.g., **81** → **80**, Scheme 11b and **82** → **83**, Scheme 11c). We have successfully employed the double enantioselective decarboxylative allylation strategy in the total synthesis of the cyathin diterpenoid cyanthiwigin F (**84**, Scheme 11c).[24d]

Mechanistic Insights

Although we have not fully elucidated the fine mechanistic details of enantiodiscrimination with the Pd•PHOX catalyst, an intriguing picture of the reaction's general mechanism has emerged from our experimental studies. A number of experimental observations suggest that the mechanism of our allylation of prochiral nucleophiles differs substantially from that of Pd•PHOX-catalyzed malonate alkylation of prochiral allyl fragments, which has been studied in detail by Helmchen[82a–d] and Pfaltz.[82e]

Helmchen's model for the asymmetric allylic alkylation of prochiral allyl electrophiles (R ≠ H, Scheme 12) with Pd•PHOX catalysts involves attack at one allyl terminus of a (PHOX)Pd-π-allyl complex by an outer-sphere malonate anion. The allyl group isomers **85** and **86** are in rapid equilibrium such that the nucleophile's preferred attack (**86**), from the open quadrant at the allyl terminus *trans* to phosphorus, is the nearly exclusive reaction pathway. The resulting Pd(0)•olefin complexes (e.g., **87**) have been observed by low temperature NMR.[82a,b] Notably, stereoinduction in such alkylation reactions suffered when the steric bulk of the allyl substituents was reduced (e.g., 96% ee when R = *i*-Pr, 71% ee when R = Me).[83] It was difficult to rationalize the high levels of stereoinduction observed in our allylation by this outer-sphere mechanism in that our substrates typically have unsubstituted allyl termini. Additionally, formation of the new stereocenter on the enolate via an outer-sphere mechanism would require the chiral Pd complex to differentiate the prochiral faces of an unassociated enolate, where steric and electronic interactions between the nucleophile and the distant chiral backbone would be minimal.[84] Moreover, a gearing effect through the allyl ligand is unlikely given the lack of sterically large groups (R = H).

In addition to these hypothetical arguments, we have made several experimental observations that do not correlate well to an outer-sphere enolate attack mechanism. The high enantioselectivity under our conditions appears to correspond with circumstances that would keep ion pairs tightly associated. The range of effective solvents found during our

optimization studies demonstrated this trend: ethereal solvents (e.g., THF), aromatic solvents (e.g., benzene), ethyl acetate, and triethylamine share few properties other than having low dielectric constants in the range of 2 to 8, but each provided products in high ee (see Table 3). In such low dielectric media, dissociative solvation of ion pairs is difficult.[85] In conjunction with the lack of other counterions in the reaction, the low dielectric value would tend to enforce an inner-sphere mechanism wherein close contact of the enolate and the chiral environment would facilitate the discrimination between the prochiral enolate faces.[86]

Based on our initial reasoning and empirical observations, we developed a working model for the course of the reaction via an inner-sphere mechanism (Scheme 13). Oxidative addition of Pd(0)•PHOX complex **88** to substrate **8** or **10** leads to [Pd(allyl)PHOX] complex **41** and carboxylate **89** or mixed carbonate **90**. We believe that an equilibrium exists between the charge-separated form and the coordination complex bearing an η^1-allyl group (e.g., **91**). We have isolated and characterized the β-ketocarboxylate analog (**91**) by X-ray crystallography and found that it can be decomposed to deliver enantioenriched ketone **9**, and therefore it appears to be an important intermediate on the reaction pathway.[87] Subsequent loss of CO_2, which is most likely Pd-assisted, leads to enolate **14** and the Pd-complex **41**. Association of these two fragments leads to 5-coordinate intermediate **92**, a compound resembling a transition state for associative substitution with the enolate bound to the sterically less-encumbered apical position of the square-planar metal. By slightly different means, allyl enol carbonate and silyl enol ether substrates may intercept the key structure **92**. Shifting of the allyl group from an η^3- to an η^1-binding mode allows the enolate fragment to move into the square plane and form intermediate **93**, thus completing the associative ligand substitution. From this complex, a standard 3-centered reductive elimination would require a shift from *O*- to *C*-bound Pd-enolate.[88] Although possible, we reasoned that this isomerization would be unfavorable due to the steric demands of the resulting tertiary palladium species. As an alternative, we postulated an extended reductive elimination pathway proceeding through a cyclic 7-membered pericyclic transition state (**94-boat** or **94-chair**) similar to a sigmatropic rearrangement.[89],[90] Importantly, situating the carbocyclic ring of the enolate fragment away from the bulky *t*Bu group of the oxazoline provides a plausible predictive model for the observed absolute sense of enantiofacial selectivity.[37] Liberation of the product ketone (**9**) from complex **95** regenerates the catalytic Pd(0) species **88**.

Typically, inner- and outer-sphere processes may be differentiated by stereochemically labeling the allyl fragment and evaluating the relative stereochemistry of the products.[91] For example, this type study was carried out by Trost and coworkers on their decarboxylative allylic alkylation system, and the results suggest an outer-sphere mechanism.[42l] However, in the present case, these experiments could not be performed because the necessary cyclic carbonates suffered from very poor reactivity and enantioselectivity. In fact, even simple substitution of the termini of acyclic allyl groups (e.g., crotyl carbonates) severely impacted reactivity and perhaps suggests that for such substrates a different mechanism is operative.[92] Given these substrate limitations, we were obliged to seek out other forms of mechanistic evidence to evaluate our proposal.

Since it is conceivable that multiple ion pairs could be involved in the transition state (e.g., an enolate bound to one [Pd(allyl)PHOX] fragment could attack the Pd-bound allyl fragment associated with another enolate), we conducted simple kinetics experiments that support a pathway involving a single metal center (Figure 1 through Figure 4).[53] Initial attempts to examine the kinetics of the reaction with respect to the Pd•PHOX complex did not give clear results. We suspect that the precision of the calculated initial rates may be complicated by inconsistent aerobic oxidation of the phosphine ligand[32] leading to some uncertainty in the

effective catalyst concentration. A fit to a rate law first-order in Pd•PHOX concentration is most consistent with the experimental observations, tentatively supporting the notion that a single metal center is involved in the mechanism (Figure 1). Additionally, the lack of an observed non-linear effect between product and ligand ee is also consistent with the action of a single metal center in the enantiodetermining step (Figure 2).[93] Interestingly, kinetic studies also found a zero-order dependence on substrate concentration in the allyl enol carbonate (Figure 3) and β-ketoester (Figure 4) cases.[94] Based on these results, we suspect that the rate-limiting step is either loss of CO_2 from a Pd-carboxylate intermediate (e.g., **91** → **41** + **14**, Scheme 13), or C–C bond formation (e.g., **93** → **95**, Scheme 13). The isolation of the relatively stable Pd-carboxylate complex **91** is indicative of a slow decarboxylation step. The longer reaction times observed with β-ketoester substrates relative to the corresponding allyl enol carbonates is also more consistent with decarboxylation as the rate determining step, as the rate difference would be attributed to the difference in breaking a C–C bond (β-ketoester) compared to a C–O bond (enol carbonate). However, we cannot rule out the possibility that different substrate classes may have different rate-determining steps.

In addition to these studies, we designed other experiments to differentiate our proposed mechanism from that elucidated by Helmchen.[82] Enolates where charge is delocalized (e.g., those derived from β-ketoesters or α-aryl ketones), and should therefore tend to form weak ion pairs, give high yields but extremely low levels of enantioselectivity (see Table 16).[96] This result suggests that, in such cases, allylation proceeds primarily via the more conventional, although in this case poorly selective, outer-sphere attack. The reactivity of sterically demanding substrates in our reaction is also inconsistent with an outer-sphere, intermolecular nucleophilic enolate attack. In a nucleophilic bimolecular reaction, such as the Helmchen allylation mechanism (Scheme 12), steric bulk near the site of bond formation typically impedes the rate of the reaction.[97] However, in our case there is little difference in the reaction time, yield, or enantioselectivity when comparing the formation of ketone **9** with more sterically demanding ketones (Figure 5). This observation is more consistent with an intramolecular reaction mechanism.

Another observation at odds with an external attack mechanism is the unusual tolerance to water (Table 18). Multiple equivalents of water introduced into the reaction have only a moderate effect on the yield of the reaction. This contrasts typical enolates, which are rapidly quenched by water even at low temperatures, and suggests that once decarboxylation occurs the intermediate enolate formed in the reaction is tightly associated with or covalently bound to its Pd counterion for most of its lifetime.[98]

In an effort to trace the fate of the allyl and enolate fragments in the course of the reaction, we performed crossover experiments with a 1:1 mixture of deuterated allyl enol carbonates **97** and **98** in THF, dioxane, and benzene (Scheme 14).[99] Analysis of the products by high-resolution mass spectrometry revealed the presence of all four possible product masses in nearly equal amounts.[100] In conjunction with the water addition experiments, this observation suggests that a palladium enol carbonate species (**41** + **90** or **41•90**) may be a long-lived intermediate. Such an intermediate would not be readily protonated by water,[101] and this delocalized anion may facilitate crossover by dissociation from the metal center. In the case of β-ketoester substrates, a β-ketocarboxylate intermediate (e.g., **91**) may play an analogous role.[102]

In order to validate our hypothesis regarding the persistence of an intermediate carboxylate or mono-alkyl carbonate (**89** or **90**, respectively), we collected ^{31}P NMR data during the reaction.[27d],[53] Non-ligated *t*Bu-PHOX (**19**) exhibited a ^{31}P resonance at −5.9 ppm. When $Pd_2(dba)_3$ and *t*Bu-PHOX were complexed, a new resonance was observed at 18.8 ppm along with excess ligand (Figure 6, spectrum A). When substrate (±)-**10** was added, the

resonance at 18.8 ppm disappeared immediately and the only observed intermediate was found at 30.9 ppm, which persisted until the end of the reaction (Figure 6, spectrum B). When the substrate was completely consumed, the initial Pd•PHOX complex returned at 18.8 ppm (Figure 6, spectrum C).[103] Interestingly, similar behavior was observed in reactions with allyl carbonate reactions, although the chemical shift of the intermediate species differed slightly.

The separately prepared [Pd(II)(allyl)(PHOX)]$^{+}$[PF_6]$^{-}$ complex (**41**, Scheme 5) exhibited two ^{31}P resonances (other than those due to PF_6^{-}) at 23.5 and 22.5 ppm in a 2:1 ratio (in THF), due to the mixture of *endo*- an *exo*-allyl isomers.[82] The different chemical shifts for this Pd(II) complex relative to that observed during the reaction suggest a different ligation environment about the Pd center. To correlate these two different species, *n*Bu_4NOAc was added to a solution of [Pd(II)(allyl)(PHOX)]$^{+}$[PF6]$^{-}$, and a new species was observed at 30.9 ppm, which matches independently synthesized [Pd(II)(allyl)(PHOX)(OAc)].[27d] Based on these experiments, we believe that the observed catalyst resting state in solution is likely the [Pd(II)(allyl)(PHOX)]$^{+}$/[carboxylate]$^{-}$ ion pair (**41** + **89**, Scheme 13) or the coordination complex **91**. Efforts to fully characterize additional intermediate structures are ongoing.

The solid-state structure of independently prepared [Pd(II)(allyl)PHOX]$^{+}$[PF_6]$^{-}$ salt **41** lends credence to the possibility of an apically bound palladium enolate. As shown in Scheme 5, after recrystallization the complex partially co-crystallizes with a molecule of ethanol in its unoccupied quadrant.[47] We envision this as the likely site of enolate coordination (e.g., apically bound enolate complex **92**, Scheme 13).

Given the body of evidence accrued in these experimental studies and our inability to probe the mechanism through classical stereochemical labeling experiments,[91] we initiated a collaboration with the Goddard group at Caltech in order to investigate the details of the mechanism via computational modeling.[75] The computational studies carried out have corroborated our initial hypothesis regarding the inner-sphere mechanism, the difficult isomerization of *O*- to *C*-bound Pd enolate, and the unusual cyclic 7-membered reductive elimination pathway (Scheme 13). Notably, these calculations have found that the traditional outer-sphere mechanism (Scheme 12) is significantly higher in energy than the inner-sphere pathway. The simulations have not yet elucidated the fine details of the origin of enantioselectivity. Experiments and computational studies to better characterize the reaction mechanism are under way with the hope of improving the enantioselectivity and scope of the asymmetric alkylation.

Conclusion

In order to address a significant deficiency in the asymmetric alkylation literature, we have developed a strategy to prepare enantioenriched cycloalkanones in high yield. This work provides direct access to valuable enantioenriched α-quaternary ketones from readily accessible enolate precursors. Critical to our success was the use of enolate precursors, which can be converted to enolates under mild conditions, and the use of a chiral catalyst that exhibited the enolate isomeric fidelity found in Tsuji's non-enantioselective system. The reactivity and enantioselectivity of the alkylation reactions have proven to be quite general with respect to substrate steric bulk, ring size, unsaturation, and diverse functional groups. We have demonstrated the relevance of the α-quaternary ketones produced in the reaction by their conversion to a number of carbocyclic chiral building blocks, including several spiro quaternary motifs, as well as in the asymmetric syntheses of several natural products. Studies directed toward further development of the scope of this reaction and catalyst system

are ongoing. Additionally, the continued application of our asymmetric alkylation as a key enantiodetermining step in natural products synthesis will be reported in due course.

Experimental Section

Representative procedure for the enantioselective decarboxylative alkylation of allyl enol carbonates

A 50 mL round-bottom flask equipped with a magnetic stir bar was flame dried under vacuum. After cooling under dry argon, $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol, 0.025 equiv) and (*S*)-*t*Bu-PHOX (**19**, 24.2 mg, 0.0625 mmol, 0.0625 equiv) were added. After the flask was flushed with argon, THF (30 mL) was added, and the contents were stirred at 25 °C for 30 min, at which time allyl enol carbonate **8** (196.2 mg, 1.0 mmol, 1.0 equiv) was added by syringe in one portion. When the reaction was complete by TLC (2 h), the reaction mixture was evaporated under reduced pressure and the residue chromatographed (2→3% Et_2O in pentane on SiO_2) to afford (*S*)-2-allyl-2-methylcyclohexanone ((*S*)-**9**) (129.6 mg, 85.1% yield, 87% ee) as a colorless oil; ^1H NMR (300 MHz, $CDCl_3$) δ 5.75-5.61 (m, 1H), 5.05 (s, 1H), 5.01 (m, 1H), 2.40-2.31 (comp. m, 3H), 2.21 (dd, *J* = 13.8, 7.5 Hz, 1H), 1.78 (comp. m, 5H), 1.56 (m, 1H), 1.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.4, 133.7, 117.9, 48.4, 41.9, 38.8, 38.5, 27.4, 22.6, 21.0; IR (Neat Film NaCl) 2934, 2865, 1707, 1451, 912 cm^{-1}; HRMS (EI) m/z calc'd for $C_{10}H_{16}O$ [M]+: 152.1201, found 152.1204; $[\alpha]_D^{21}$ −49.64 (c 2.38, hexane, 98% ee).

Representative procedure for the enantioselective decarboxylative alkylation of silyl enol ethers

A 50 mL round-bottom flask equipped with a magnetic stir bar was flame dried under vacuum. After cooling under dry argon, $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol, 0.025 equiv), (*S*)-*t*Bu-PHOX (**19**, 24.2 mg, 0.0625 mmol, 0.0625 equiv), and TBAT (189 mg, 0.35 mmol, 0.35 equiv) were added. After the flask was flushed with argon, THF (30 mL) was added, and the contents were stirred at 25 °C for 30 min, at which time diallyl carbonate (150.6 μL, 1.05 mmol, 1.05 equiv) and silyl enol ether **SI23** (184.35 mg, 1.0 mmol, 1.0 equiv) were added sequentially by syringe in single portions. When the reaction was complete by TLC (2 h), the reaction mixture was evaporated under reduced pressure and the residue chromatographed (2→3% Et_2O in pentane on SiO_2) to afford ketone (*S*)-**9** (144.3 mg, 94.8% yield, 87% ee).

Representative procedure for the enantioselective decarboxylative alkylation of β-ketoesters

A 100 mL rb flask was equipped with a magnetic stir bar and flame dried under vacuum. After cooling under dry nitrogen, $Pd_2(dba)_3$ (22.9 mg, 0.025 mmol, 0.025 equiv) and (*S*)-*t*Bu-PHOX (**19**, 24.2 mg, 0.0625 mmol, 0.0625 equiv) were added. The flask containing the solids was evacuated for 15 min and then refilled with dry nitrogen. Dry THF (30 mL) was then added and the resulting solution stirred at 25 °C for 30 min. At this point, allyl 1-methyl-2-oxocyclohexanecarboxylate ((±)-**10**) was added via syringe in one portion. When the reaction was complete by TLC (7.5 h), the reaction mixture was evaporated under reduced pressure and the residue purified by column chromatography (SiO_2, 1.5→2.5% Et_2O in pentane) to afford ketone (*S*)-**9** (129.6 mg, 85% yield, 88% ee).

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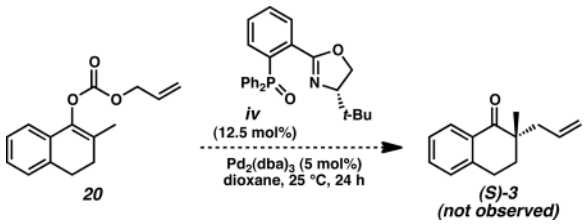
30. THF also offers the practical advantage of being easier to obtain pure and dry than dioxane. The lower boiling point of THF also aided in isolation of volatile ketones like **9**.

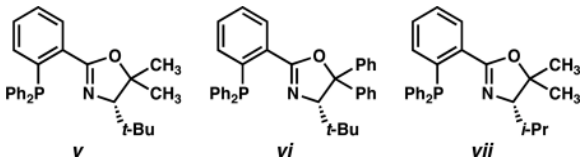
31. The rate and selectivity of the reaction are typically unchanged when Pd(0) sources other than $Pd_2(dba)_3$ are used (e.g., bis(di(3,5-dimethoxybenzylidene)acetone)palladium(0) ($Pd(dmdba)_2$) and tris(di(4-methoxybenzylidene)acetone)dipalladium(0) ($Pd_2(pmdba)_3$)). For a singular case in which the choice of Pd(0) source affected conversion, see: White DE, Stewart IC, Seashore-Ludlow BA, Grubbs RH, Stoltz BM. Tetrahedron. 2010; 66:4668–4686. [PubMed: 20798895] For a discussion of the utility of $Pd(dmdba)_2$ and $Pd_2(pmdba)_3$, see ref 48.

32. We have studied the ^{31}P NMR spectra of the reaction at length (see Figure 6 and Supporting Information), and we believe that phosphine oxide iv is produced as a catalyst decomposition product when O_2 is present. In the absence of Pd PHOX ligand **19** does not oxidize significantly in the solid state or in solution. Phosphine oxide **iv** may be observed during the reaction by ^{31}P NMR (27 ppm) in typical experiments prepared on the benchtop. Typically, the rate of ligand oxidiation is slow relative to the time frame of the decarboxylative alkylation (<12 h) and reactions may be carried out routinely on the benchtop under inert atmosphere in dry degassed solvents. Substrates that are particularly slow to react are often more efficiently converted to products in a glovebox to extend the lifetime of the catalyst (Figure 6 shows virtually no ligand oxidation occurs when the reaction is rigorously protected from air). We have independently synthesized *S*-*t*Bu-PHOX oxide (**iv**) and found that when used as a ligand for the conversion of tetralone-derived allyl enol carbonate **19** to ketone **3** no reaction was observed:

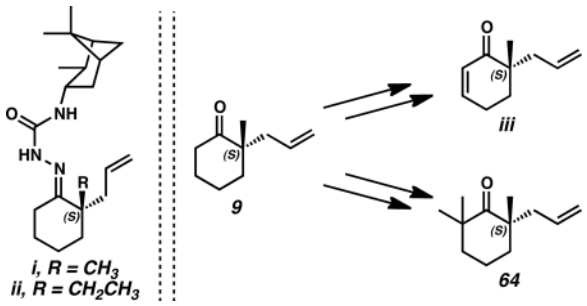
Supporting information for this article is available on the WWW under http://www.chemeurj.org/ or from the author.



33. As a result of our desire to generate a large variety of PHOX ligands, we adapted a procedure for C–P bond formation disclosed by Buchwald and coworkers for the synthesis of PHOX ligands, see: Tani K, Behenna DC, McFadden RM, Stoltz BM. Org. Lett. 2007; 9:2529–2531. [PubMed: 17536810] Krout MR, Mohr JT, Stoltz BM. Org. Synth. 2009; 86:181–193. [PubMed: 20072718] Gelman D, Jiang L, Buchwald SL. Org. Lett. 2003; 5:2315–2318. [PubMed: 12816437] d) For an alternative cross-coupling with phosphine oxides, see: McDougal NT, Streuff J, Mukherjee H, Virgil SC, Stoltz BM. Tetrahedron Lett. 2010; 51:5550–5554. [PubMed: 21076623]
34. Synthesized in analogy to PHOX ligands prepared by Helmchen, see ref 29c.
35. We have additionally prepared the similar ligands **v** and **vi**. In our prototypical reaction (**8** → **9**) 86% and 79% ee product was formed, respectively, with complete substrate conversion. A recent publication from another laboratory has put forth the related ligand **vii**, that is available from valine, as an alternative to *t*Bu-PHOX. The authors report comparable levels of enantioinduction with fluorinated enol silane substrates. See: Bélanger É, Pouliot M-F, Paquin J-F. Org. Lett. 2009; 11:2201–2204. [PubMed: 19388656]

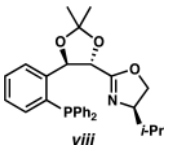


36. Wiese B, Helmchen G. Tetrahedron Lett. 1998; 39:5727–5730.
37. a) To definitively assign the absolute stereochemistry of the newly formed quaternary stereocenter, we prepared the corresponding semicarbazones **i** and **ii**, each bearing an isopinocampheylamine portion of known configuration, which were then characterized by X-ray crystallography. In addition, we converted ketone **9** to cycloalkanones **iii** and **64**, which matched the major enantiomer of products formed in the direct allylation reactions (see Supporting Information for details). The *S* configuration of tetralone **3** was confirmed by comparison with literature data (see ref 16b). Based on the consistent sense of enantiofacial selectivity, the stereochemistries of the remaining allylation products are inferred by analogy.



b) The recrystallization of semicarbazone derivatives as a means to increase the ee of our products has proven to be of general use with the α-quaternary ketones and their derivatives. For an example, see: ref 24a. c) For an optimized procedure for the preparation and recrystallization of the semicarbazone (a single recrystallization from toluene provided material of 98% ee), see: Mohr JT, Krout MR, Stoltz BM. Org. Synth. 2009; 86:194–211. [PubMed: 21197146]

38. Trudeau and Morken synthesized PHOX-like ligand **viii** as well as some structurally related ligands. These were tested it in a decarboxylative alkylation with carbonate substrate **20**, providing ketone **3** in up to 59% ee. See: Trudeau S, Morken JP. Tetrahedron. 2006; 62:11470–11476.



39. These reactions were carried out before the optimal solvent and concentration (THF at 0.031M) were determined. We believe that reexamining these reactions under the optimized reaction conditions would not significantly change the outcome, as only increases in ee and yield would be anticipated
40. Dawson GJ, Frost CG, Martin CJ, Williams JMJ, Coote SJ. Tetrahedron Lett. 1993; 34:7793–7796.
41. Smidt SP, Menges F, Pfaltz A. Org. Lett. 2004; 6:2023–2026. [PubMed: 15176809]
42. Subsequent to our initial report on asymmetric allylation, several related reports have appeared: a) For a collected review see ref 27g Trost BM, Xu J. J. Am. Chem. Soc. 2005; 127:2846–2847. [PubMed: 15740108] Nakamura M, Hajra A, Endo K, Nakamura E. Angew. Chem. 2005; 117:7414–7417. Angew. Chem., Int. Ed. 2005; 44:7248–7251. Trost BM, Xu J. J. Am. Chem. Soc. 2005; 127:17180–17181. [PubMed: 16332054] Burger EC, Barron BR, Tunge JA. Synlett. 2006:2824–2826. Trost BM, Bream RN, Xu J. Angew. Chem. 2006; 118:3181–3184. Angew. Chem., Int. Ed. 2006; 45:3109–3112. Trost BM, Xu J, Reichle M. J. Am. Chem. Soc. 2007; 129:282–283. [PubMed: 17212401] Bélanger É, Cantin K, Messe O, Tremblay M, Paquin J-F. J. Am. Chem. Soc. 2007; 129:1034–1035. [PubMed: 17263376] Schulz SR, Blechert S. Angew. Chem. 2007; 119:4040–4044. Angew. Chem., Int. Ed. 2007; 46:3966–3970. Bélanger É, Houzé C,

Guimond N, Cantin K, Paquin J-F. Chem. Commun. 2008:3251–3253. Trost BM, Xu J, Schmidt T. J. Am. Chem. Soc. 2009; 131:18343–18357. [PubMed: 19928805] l) ref 35 and ref 38

43. Reactions below 10 °C typically do not show conversion to product, and are only reliably performed with highly activated substrates. For an example, see: Goodwin NT. Ph.D. Thesis. 2006 Jul.Pasadena, CACalifornia Institute of Technology
44. Although isomerically pure enol carbonates and silyl enol ethers were desired for substrate characterization and to maximize the yield of α-quaternary ketone, it should be noted that this is not required for the allylation reaction. The less substituted enolate precursors are cleanly transformed to 2,6-substituted ketones, which are typically readily removed by chromatography, and have no effect on the ee of the desired product.
45. Sodium and potassium methoxide (1 equiv) could be used directly as silyl enol ether activators. However, lower yields (14% and 36%, respectively) and slightly lower ee (81% and 80%, respectively) were observed.
46. For procedure, see: Liu S, Müller JFK, Neuburger M, Schaffner S, Zehnder M. J. Organomet. Chem. 1997; 549:283–293.
47. PF_6^- counterions removed for clarity. Two out of four of the crystallographically unique (Pd(allyl)PHOX) complexes in the unit cell crystallized with a molecule of ethanol. The *endo*- and *exo*-allyl isomers were present in essentially equal electron density and are modeled as a superposition of the two isomers.
48. In some cases we have encountered difficulty in separating the cycloalkanone products from the residual dba introduced with the palladium source. As a practical consideration, it is often useful to employ bis(di(3,5-dimethoxybenzylidene)acetone)palladium(0) ($Pd(dmdba)_2$) or tris(di(4-methoxybenzylidene)acetone)dipalladium(0) ($Pd_2(pmdba)_3$) as the source of palladium because of the difference in polarity of dmdba and pmdba relative to dba.
49. Coppola, GM.; Schuster, HF. α-Hydroxy Acids in Enantioselective Syntheses. Weinheim: Wiley-VCH; 1997.
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52. The corresponding trimethylsilyl enol ethers were relatively unstable and often could not be purified in high yield by silica gel chromatography. Comparable yield and ee could be obtained when the TMS enol ethers were employed in the allylation reaction. See the Supporting Information for details.
53. See the Supporting Information for details.
54. Michael A, Wolgast K. Chem. Ber. 1909; 42:3176–3177.
55. For a discussion of double stereodifferentiation, see: Eliel EL, Wilen SH, Mander LN. Stereochemistry of Organic Compounds. 1994New YorkWiley:965–971.
56. Aliquots taken during the reaction with β-ketoester (±)–**10** at 30 °C in THF show the starting material reaches a maximum of 5% ee at 83% conversion for a k_{rel} of 1.1.
57. Presumably, this is the result of the cleavage of a C–C bond during decarboxylation, rather than C–O bond found in carbonates. The exact nature of the rate-determining step of the reaction has not yet been elucidated.
58. For reviews, see: Noyori R, Tokunaga M, Kitamura M. Bull. Chem. Soc. Jpn. 1995; 68:36–56. Stecher H, Faber K. Synthesis. 1997:1–16. Huerta FF, Minidis ABE, Bäckvall J-E. Chem. Soc. Rev. 2001; 30:321–331. Pellissier H. Tetrahedron. 2003; 59:8291–8327. e) For representative stereomutative examples, see: Pfaltz A, Lautens M. Jacobsen EN, Pfaltz A, Yamamoto H. Comprehensive Asymmetric Catalysis. 1999; Vol. 2New YorkSpringer:833–884. Trost BM, Bunt RC, Lemoine RC, Calkins TL. J. Am. Chem. Soc. 2000; 122:5968–5976.
59. This hypothesis has been experimentally supported for non-enantioselective systems, see: Tsuji J, Yamada T, Minami I, Yuhara M, Nisar M, Shimizu I. J. Org. Chem. 1987; 52:2988–2995. Detalle

J-F, Riahi A, Steinmetz V, Hénin F, Muzart J. J. Org. Chem. 2004; 69:6528–6532. [PubMed: 15387574]

60. For a highlight of recent approaches to catalytic enantioselective stereoablative reactions, see: Mohr JT, Ebner DC, Stoltz BM. Org. Biomol. Chem. 2007; 5:3571–3576. [PubMed: 17971984]
61. For representative examples of stereoablative enantioconvergent catalysis, see: Hamada T, Chieffi A, Åhman J, Buchwald SL. J. Am. Chem. Soc. 2002; 124:1261–1268. [PubMed: 11841295] Mase N, Tanaka F, Barbas CF III. Angew. Chem. 2004; 116:2474–2477. Angew. Chem., Int. Ed. 2004; 43:2420–2423. Fischer C, Fu GC. J. Am. Chem. Soc. 2005; 127:4594–4595. [PubMed: 15796523] Raheem IT, Thiara PS, Peterson EA, Jacobsen EN. J. Am. Chem. Soc. 2007; 129:13404–13405. [PubMed: 17941641] Nishimura T, Katoh T, Takatsu K, Shintani R, Hayashi T. J. Am. Chem. Soc. 2007; 129:14158–14159. [PubMed: 17963393] Enders D, Narine AA, Toulgoat F, Bisschops T. Angew. Chem. 2008; 120:5744–5748. Angew. Chem., Int. Ed. 2008; 47:5661–5665.
62. Although only trace β-elimination was observed with this substrate, substrates with better leaving groups (e.g., OAc) predominantly underwent β-elimination to the αβ-unsaturated compounds.
63. Fluorinated compounds have gained frequent use in medicinal chemistry, see: Zoute L, Audouard C, Plaquevent J-C, Cahard D. Org. Biomol. Chem. 2003; 1:1833–1834. [PubMed: 12945759] Nagai K, Davies TA, Dewasse BE, Jacobs MR, Appelbaum PC. J. Antimicrob. Chemother. 2001; 48:365–374. [PubMed: 11533001]
64. For an optimized large-scale procedure, see ref 37c.
65. Increased enantiomeric excess was also observed with a Trost ligand-derived catalyst when the central position of the allyl fragment was substituted, see: ref 15l.
66. A similar increase in reactivity for vinylogous thioester substrates was observed with a Trost ligand-derived catalyst, see: ref 42f.
67. For similar approaches to the synthesis of tertiary stereocenters α to carbonyls by Trost and coworkers, see: a) Trost BM, Lehr K, Michaelis DJ, Xu J, Buckl AK. J. Am. Chem. Soc. 2010; 132:8915–8917. [PubMed: 20550121] b) ref 42d c) ref 42g
68. Under our conditions we found that negligible racemization of α-aryl ketone **49** was observed when it was allowed to remain under the reaction conditions for an additional 12 h.
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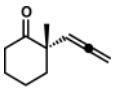
73. In addition to α-propargylated ketone **48**, trace amounts of (*S*)-allene **ix** are produced in 56% ee with ligand **23**.



ix

74. Careful tuning of the phosphine electronics in the PHOX framework could improve these results somewhat. See: McDougal NT, Virgil SC, Stoltz BM. Synlett. 2010:1712–1716. [PubMed: 21072327]

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84. Although such an outer-sphere mechanism seemed improbable to us, a priori, decarboxylative allylic alkylation experiments involving stereochemically labeled allyl fragments and catalyzed by a Pd•Trost ligand complex suggest that an outer-sphere mechanism is operative in that system, see: a) ref 42b and 42l; b) ref 86.

85. For Trost's related system, a solvent-caged ion pair was proposed based on a lack of crossover between enolate and alkyl fragments (ref 42b). However, we observed very different results from crossover experiments on our system (Scheme 10), suggesting that the details of the mechanism between these two systems may be substantially different. In later studies (ref 42l), Trost and coworkers did observe crossover in a similar experiment, although an explanation for the differing results in ref 42b was not provided.

86. Unusual patterns in enantioselectivity in Trost ligand-based asymmetric allylation systems have led Trost and coworkers to consider allylation mechanisms involving a metal-coordinated enolate as well, see: a) refs 42b and 42l; Trost BM, Zhang Y. J. Am. Chem. Soc. 2006; 128:4590–4591. [PubMed: 16594693] c) Recently, Lloyd-Jones, Norrby, and coworkers have postulated a mechanism involving hydrogen bonding of the enolate to the ligand, but not the coordination of the enolate directly to palladium, see: Butts CP, Filali E, Lloyd-Jones GC, Norrby P-O, Sale DA, Schramm Y. J. Am. Chem. Soc. 2009; 131:9945–9957. [PubMed: 19435358]

87. The crystals are composed of two diastereomeric carboxylate complexes. For clarity, only one of these is shown in Scheme 13. See: ref 27d.

88. For representative examples of *O*- and *C*-bound Pd-enolates, see: Burkhardt ER, Bergman RG, Heathcock CH. Organometallics. 1990; 9:30–44. Balegroune F, Grandjean D, Lakkisb D, Matt D. J. Chem. Soc., Chem. Commun. 1992:1084–1085. Byers PK, Canty AJ, Skelton BW, Traill PR, Watson AA, White AH. Organometallics. 1992; 11:3085–3088. Veya P, Floriani C, Chiesi-Villa A, Rizzoli C. Organometallics. 1993; 12:4899–4901. Sodeoka M, Tokunoh R, Miyazaki F,

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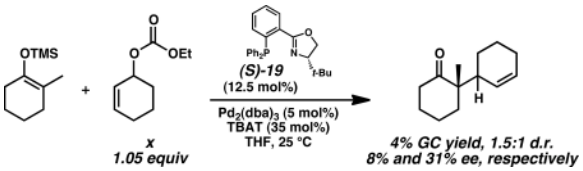
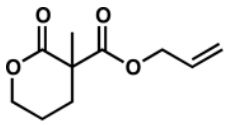
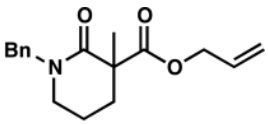
89. Similar transition states have been proposed previously for C–C bond formation, see: Kitching W, Sakakiyama T, Rappoport Z, Sleezer PD, Winstein S, Young WG. J. Am. Chem. Soc. 1972; 94:2329–2335. Méndez M, Cuerva JM, Gómez-Bengoa E, Cárdenas DJ, Echavarren AM. Chem. Eur. J. 2002; 8:3620–3628. [PubMed: 12203288]
90. Similar transition states have been proposed previously for C–O bond formation, see: Bäckvall J-E, Nordberg RE, Björkman EE, Moberg C. J. Chem. Soc., Chem. Commun. 1980:943–944. Bäckvall J-E, Nordberg RE, Wilhelm D. J. Am. Chem. Soc. 1985; 107:6892–6898. Grennberg H, Langer V, Bäckvall J-E. J. Chem. Soc., Chem. Commun. 1991:1190–1192.
91. For representative examples, see: Trost BM, Verhoeven TR. J. Org. Chem. 1976; 41:3215–3216. Trost BM, Verhoeven TR. J. Am. Chem. Soc. 1980; 102:4730–4743. Bäckvall J-E, Nordberg RE. J. Am. Chem. Soc. 1981; 103:4959–4960. Bäckvall J-E, Nordberg RE, Vågberg J. Tetrahedron Lett. 1983; 24:411–412. Keinan E, Roth Z. J. Org. Chem. 1983; 48:1769–1772. Sheffy FK, Stille JK. J. Am. Chem. Soc. 1983; 105:7173–7175. Sheffy FK, Godschalx JP, Stille JK. J. Am. Chem. Soc. 1984; 106:4833–4840. Tsuji Y, Funato M, Ozawa M, Ogiyama H, Kajita S, Kawamura T. J. Org. Chem. 1996; 61:5779–5787. Rayabarapu DK, Tunge JA. J. Am. Chem. Soc. 2005; 127:13510–13511. [PubMed: 16190710]
92. A representative experiment with a cyclic carbonate is shown below. For the preparation of carbonate **x**, see: Genêt J-P, Jugé S, Achi S, Mallart S, Ruiz-Montès J, Levif G. Tetrahedron. 1988; 44:5263–5275.



93. For discussions of non-linear effects, see: Guillaneux D, Zhao S-H, Samuel O, Rainford D, Kagan HB. J. Am. Chem. Soc. 1994; 116:9430–9439. Avalos M, Babiano R, Cintas P, Jiménez JL, Palacios JC. Tetrahedron: Asymmetry. 1997; 8:2997–3017. Girard C, Kagan HB. Angew. Chem. 1998; 110:3088–3127. Angew. Chem., Int. Ed. 1998; 37:2922–2959. Kagan HB. Synlett. 2001:888–899. Satyanarayana T, Abraham S, Kagan HB. Angew. Chem. 2009; 121:464–503. Angew. Chem., Int. Ed. 2009; 48:456–494.
94. We believe that the slight curvature in the data plots shown in Figures 3 and 4 are the result of catalyst decomposition during the reaction. Attempts to fit the data to higher order polynomial expressions were not productive.
95. For these experiments *i*Pr-PHOX was used because of the availability of both enantiomers of valine at approximately the same cost.
96. Substrates that would lead to highly basic enolate intermediates, such as lactone **xi** and lactam **xii**, have been problematic, presumably because decarboxylation is slow.

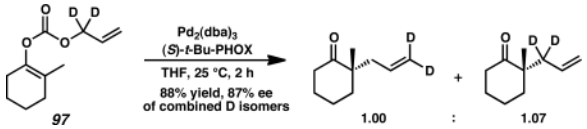


xi



xii

97. For example, replacement of the CH_2 group of the malonate nucleophile with CH(NHAc) increased reaction time from 1 h to 3–4 days. See ref 83.
98. Also consistent with the intermediacy of a Pd-bound enolate, stronger acids (e.g., formic acid) may be employed in order to achieve an enantioselective *protonation* reaction. In addition, activated Michael acceptors can be employed to achieve enantioselective conjugate addition/alkylation cascades. However, empirical observations indicate that the mechanism of C–H and C–C bond formation with these alternate electrophiles differs significantly from that of C–C bond formation in the case of allyl electrophiles, see: a) ref 71. b) ref 27e.
99. A separate reaction with dideuterio allyl enol carbonate **97** confirms that the allyl termini are scrambled during the course of the reaction. See the Supporting Information for details.



100. Although the total ion counts are not rigorously quantitative, they are consistent with the presence of all four masses in nearly equal proportions. The slight excess of the 155 *m/z* ion is likely due to the natural abundance of ^{13}C present in the dideuterio product.
101. The pK_a of related monomethyl carbonic acid has been estimated at 2.92 (H_2O solvent, 25 °C), see: Guthrie JP. Can. J. Chem. 1978; 56:2342–2354.
102. Saegusa suggested similar crossover pathways in a related, non-enantioselective system using a $Pd(PPh_3)_4$ catalyst. See ref 21b.
103. If the reaction mixture is exposed to air *t*Bu-PHOX is cleanly converted to the corresponding phosphine oxide. Pd catalyzes this conversion. See the Supporting Information for details.

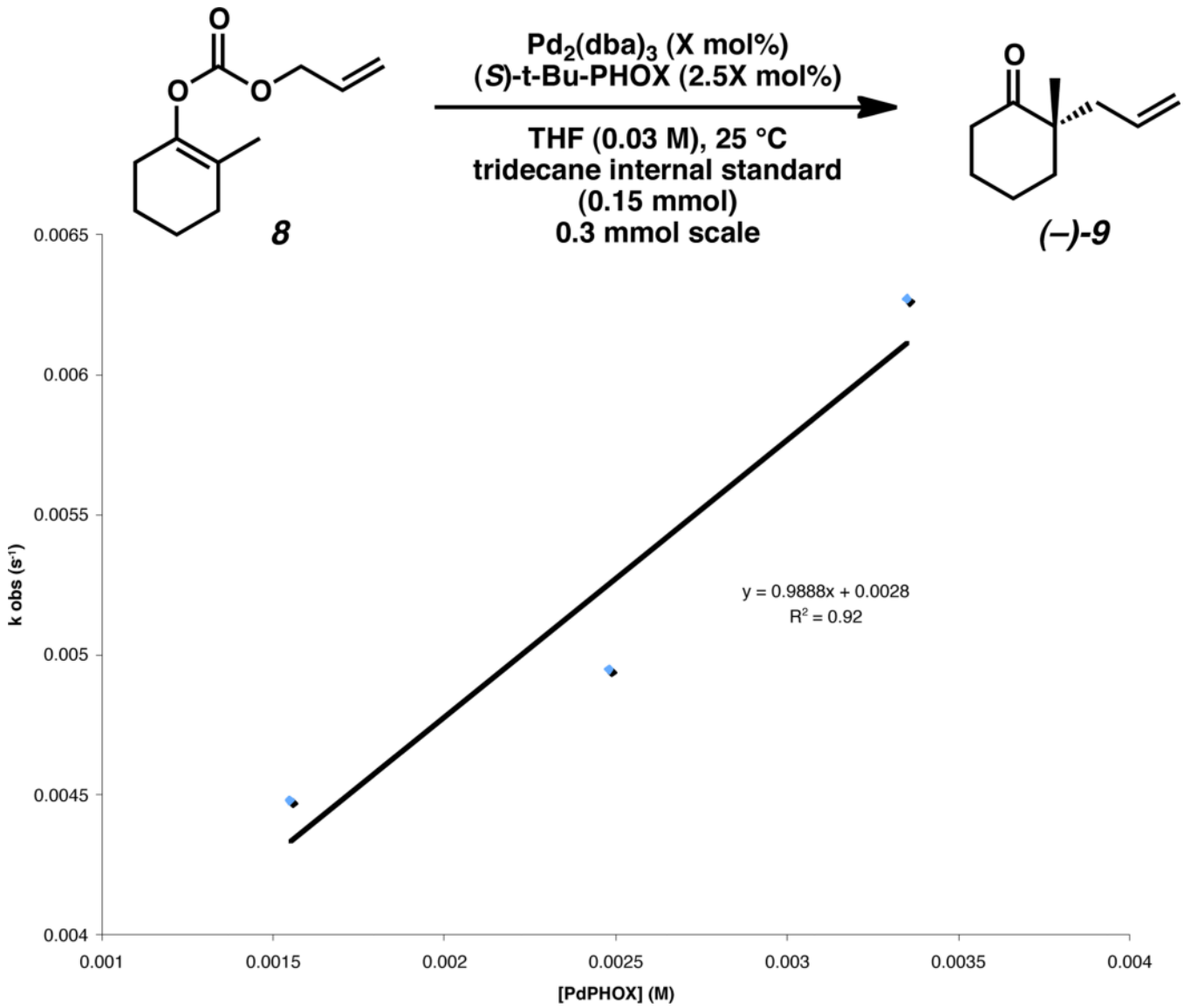


Figure 1.
Plot of k_{obs} vs. Concentration of Pd(PHOX) Complex for an Allyl Enol Carbonate.

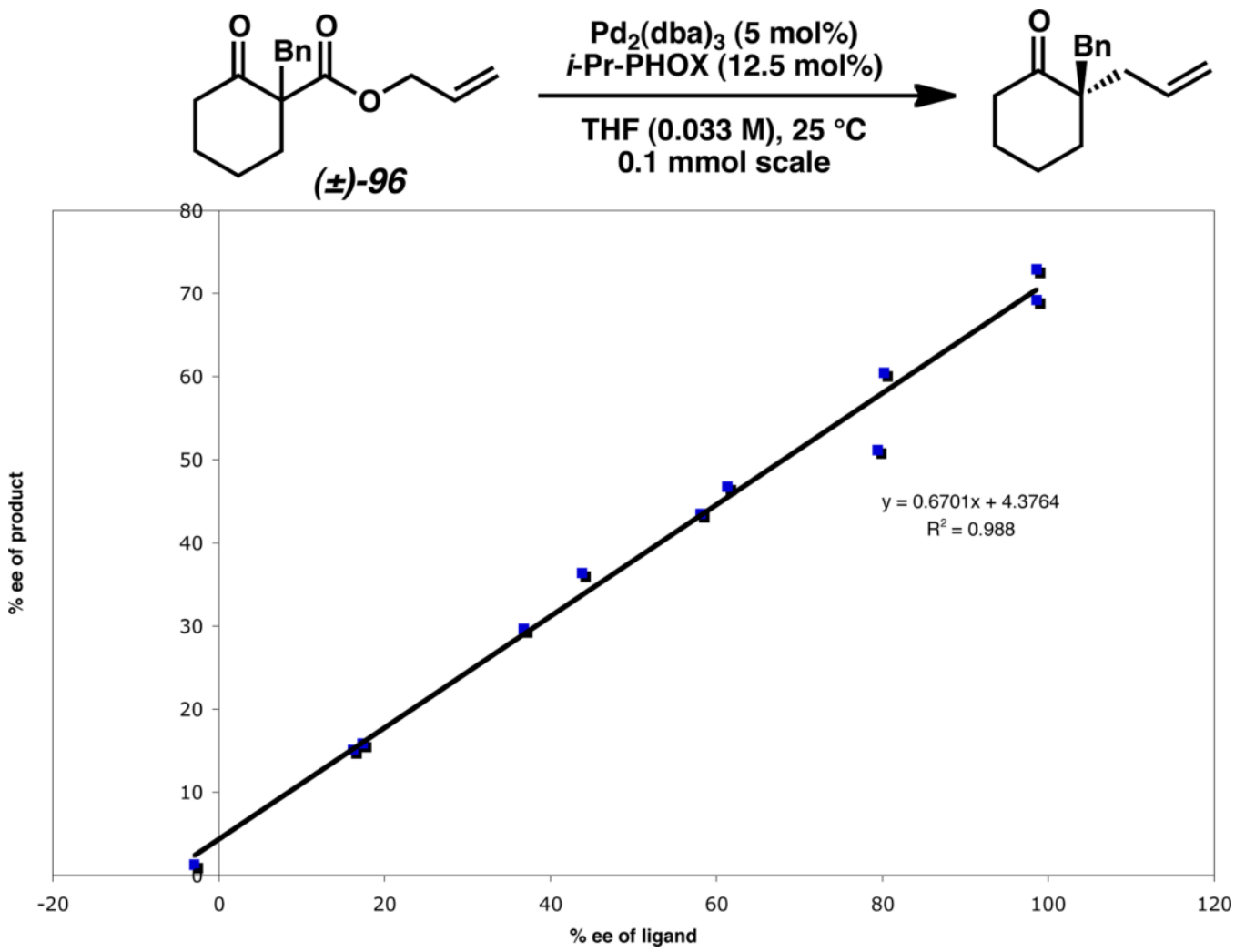


Figure 2.
Plot of *i*Pr-PHOX ee vs. Product ee.[95]

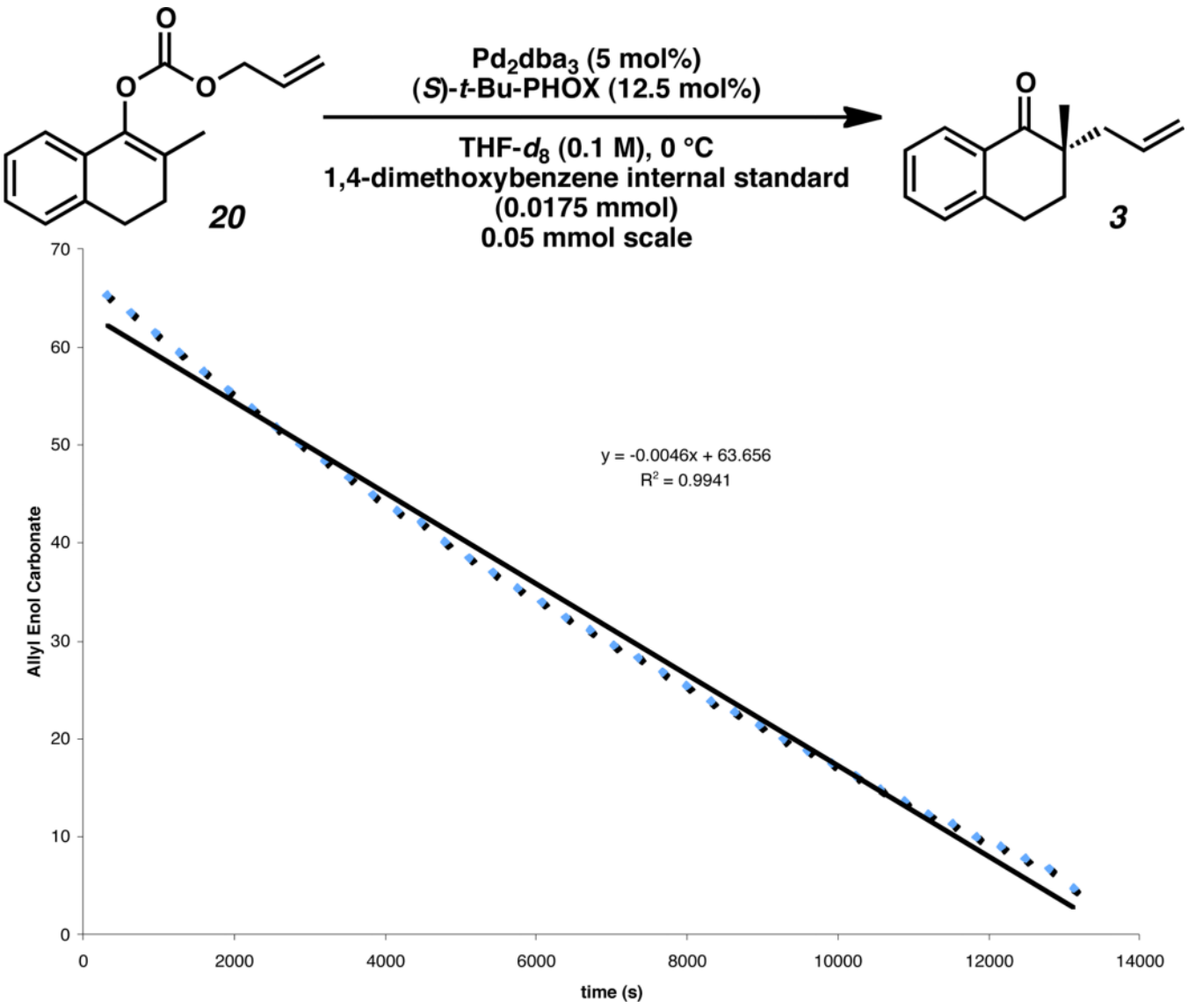


Figure 3.
Plot of Allyl Enol Carbonate ^{1}H NMR Integral vs. Time (s).

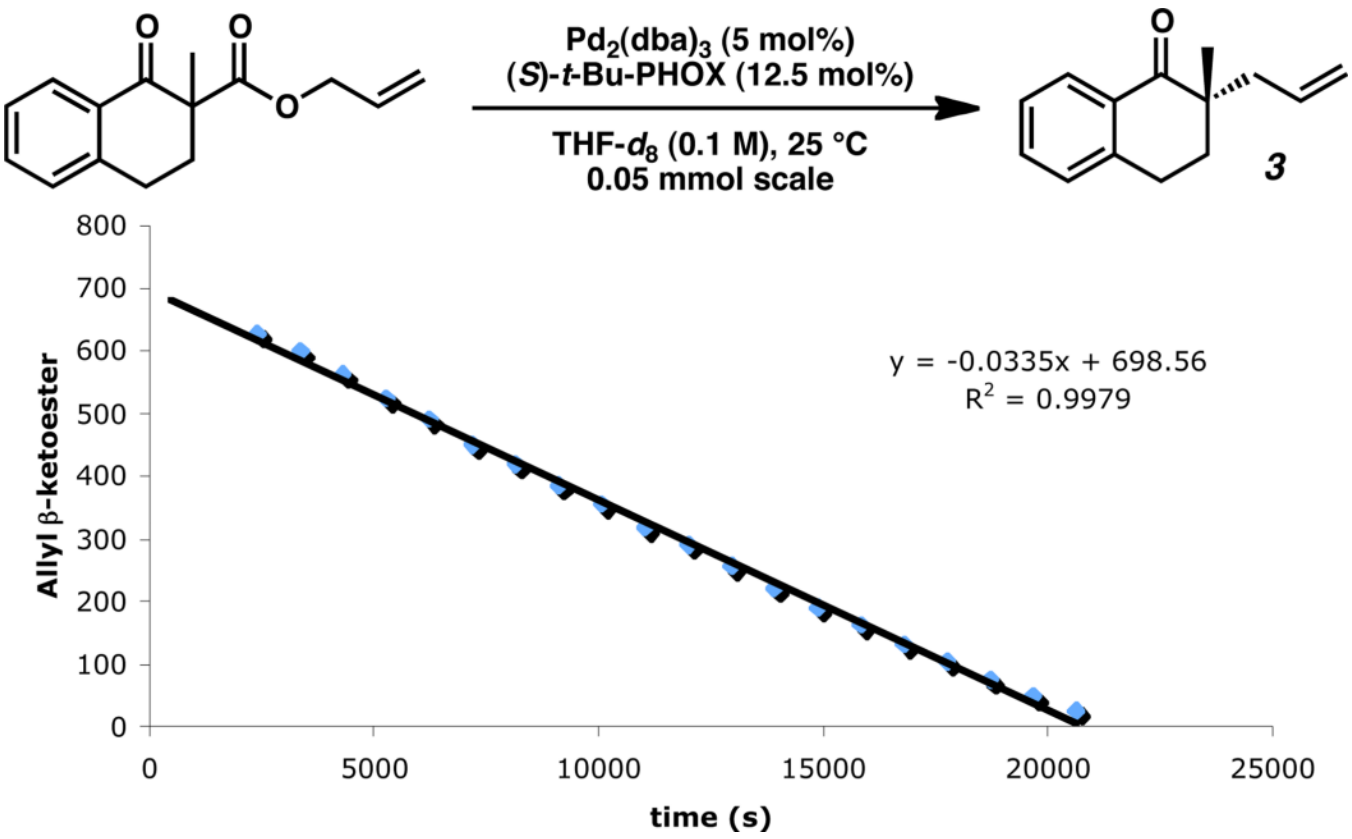


Figure 4.
Plot of Allyl β-Ketoester ^{1}H NMR Integral vs. Time (s).

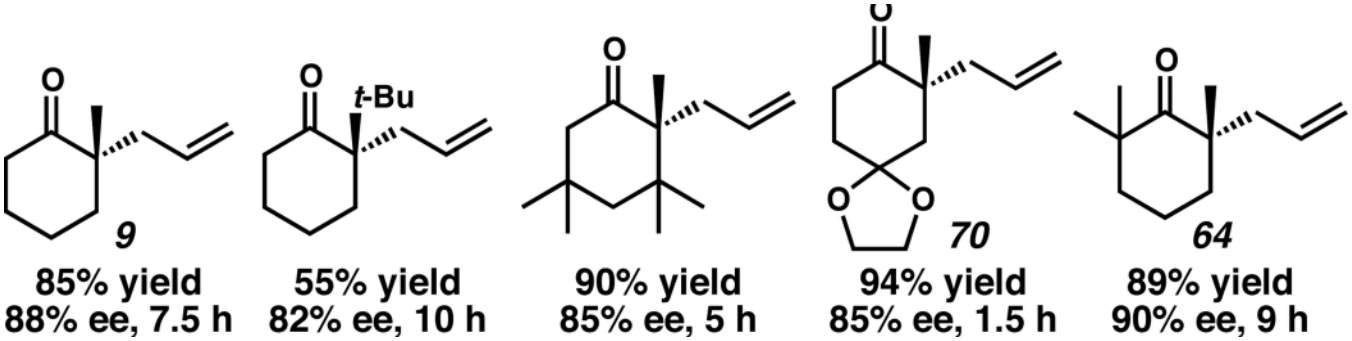


Figure 5.
Comparison of Sterically Varied Products Formed at 25 °C in THF.

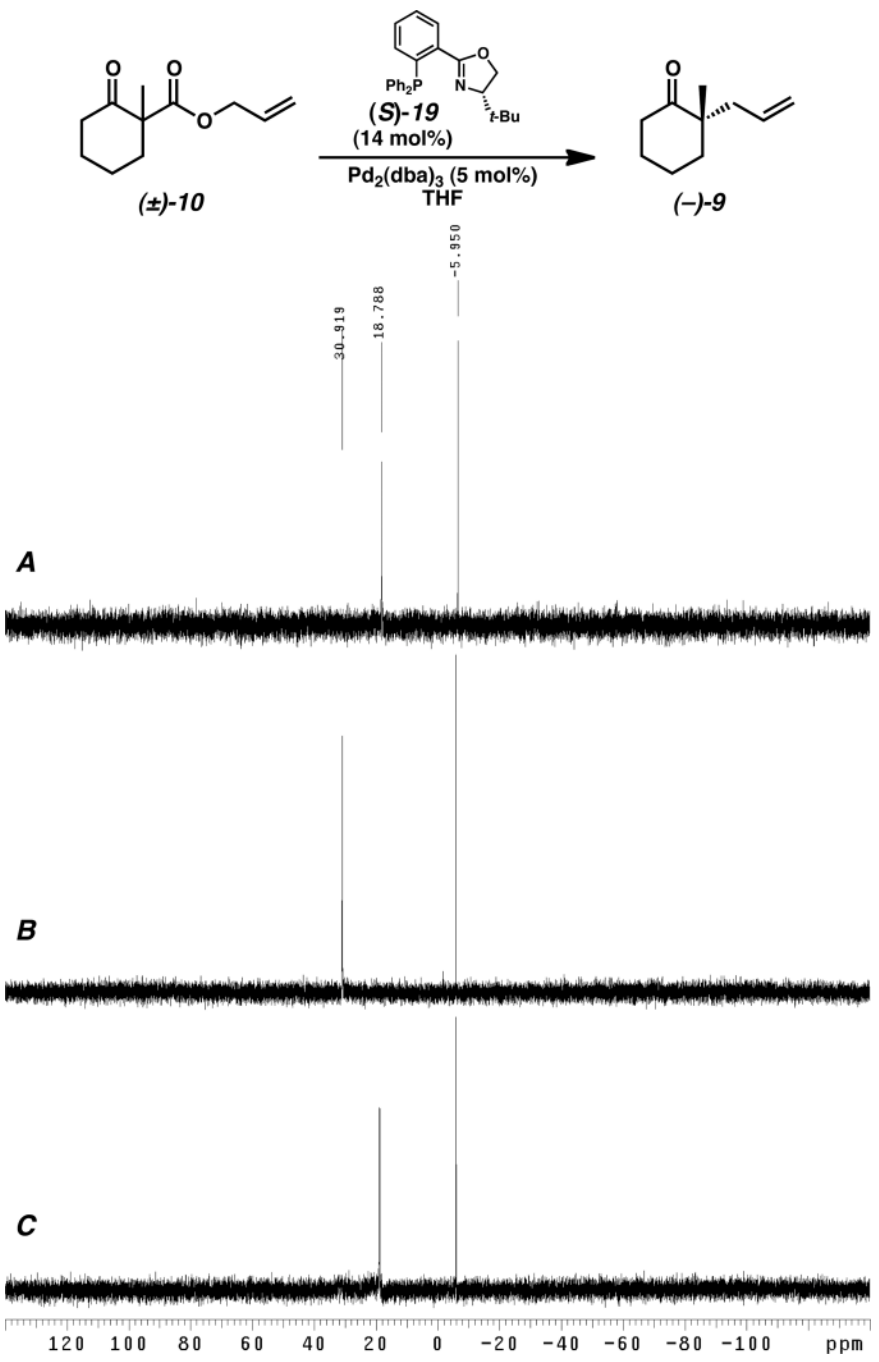
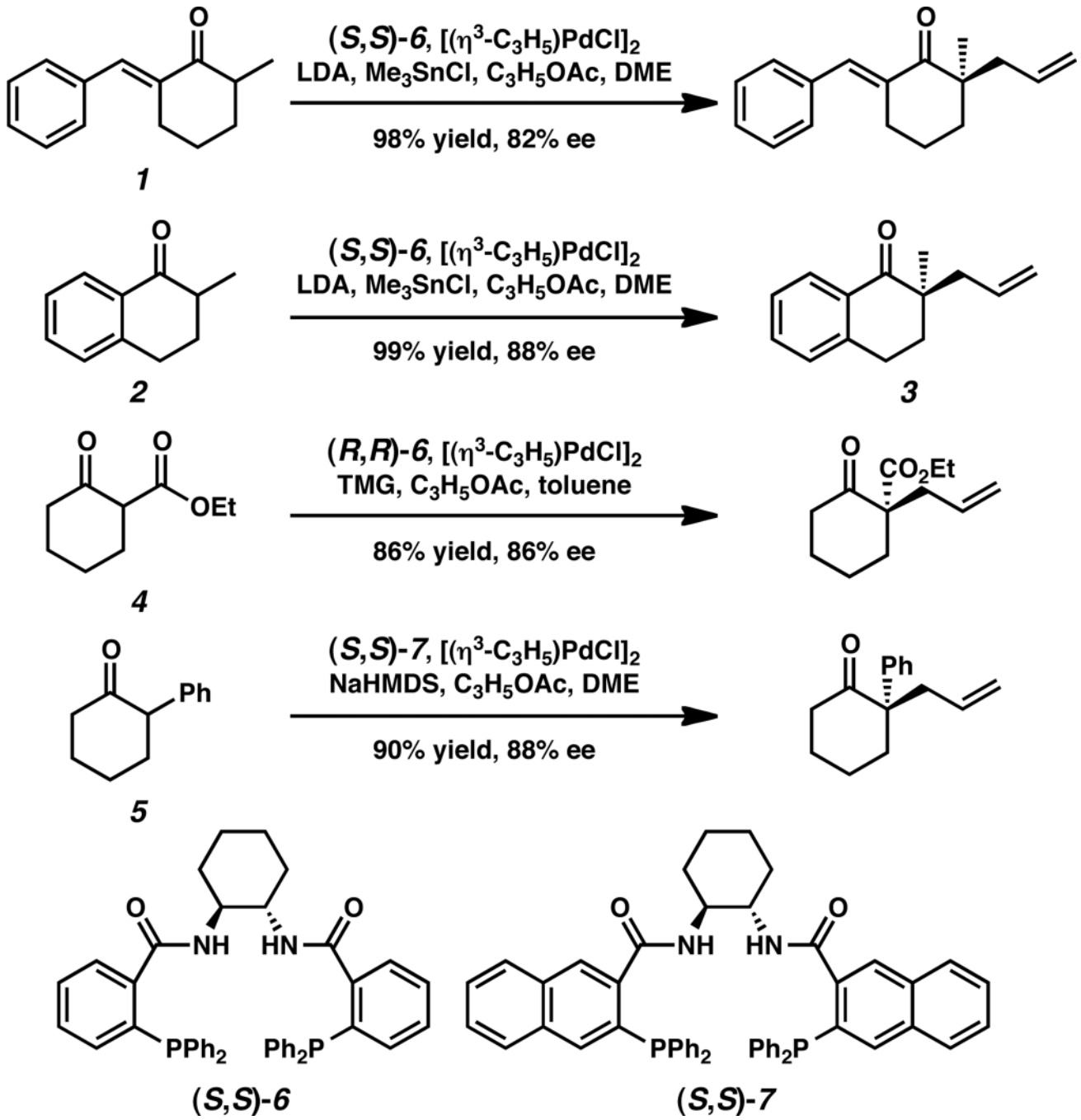
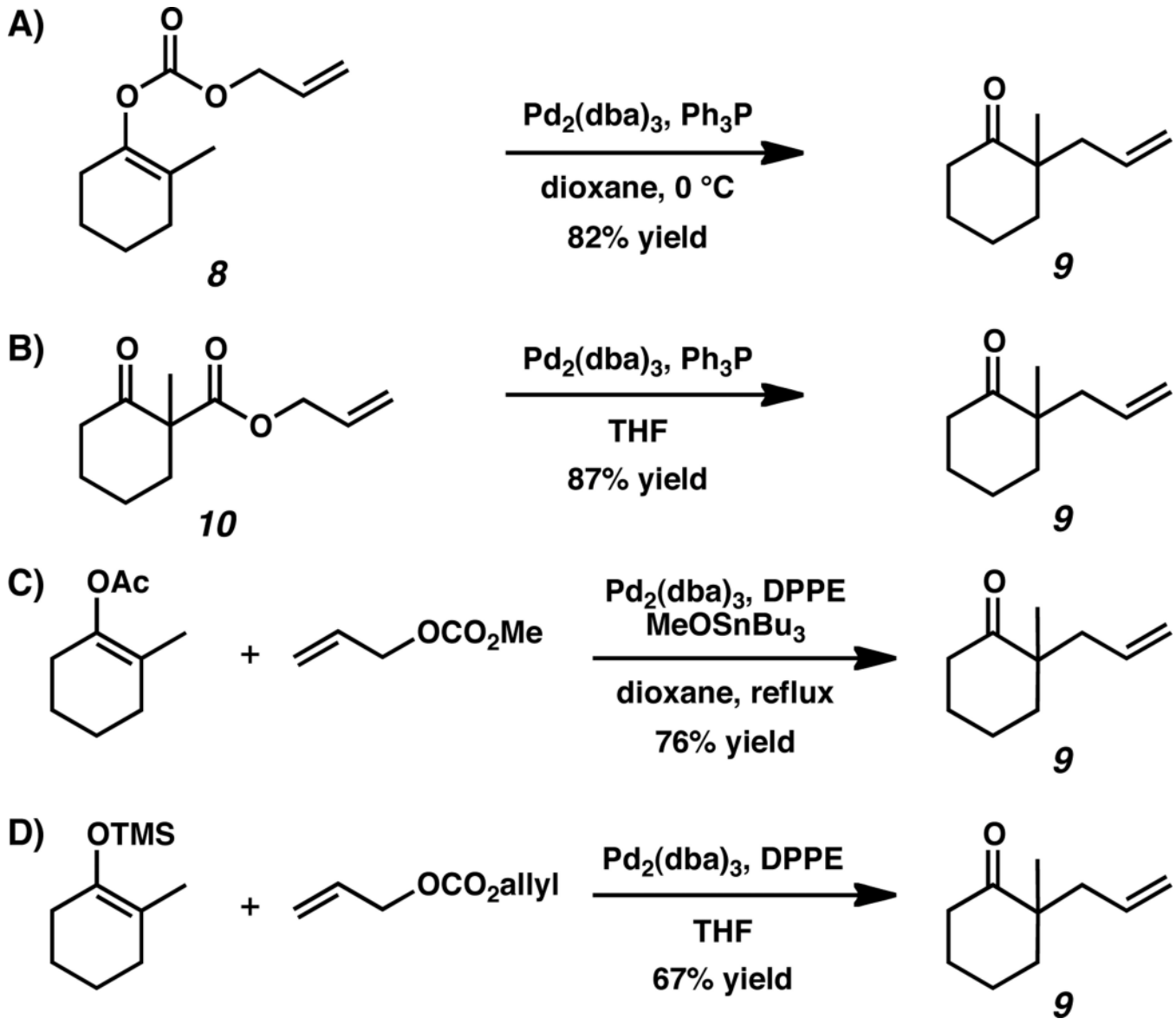


Figure 6.

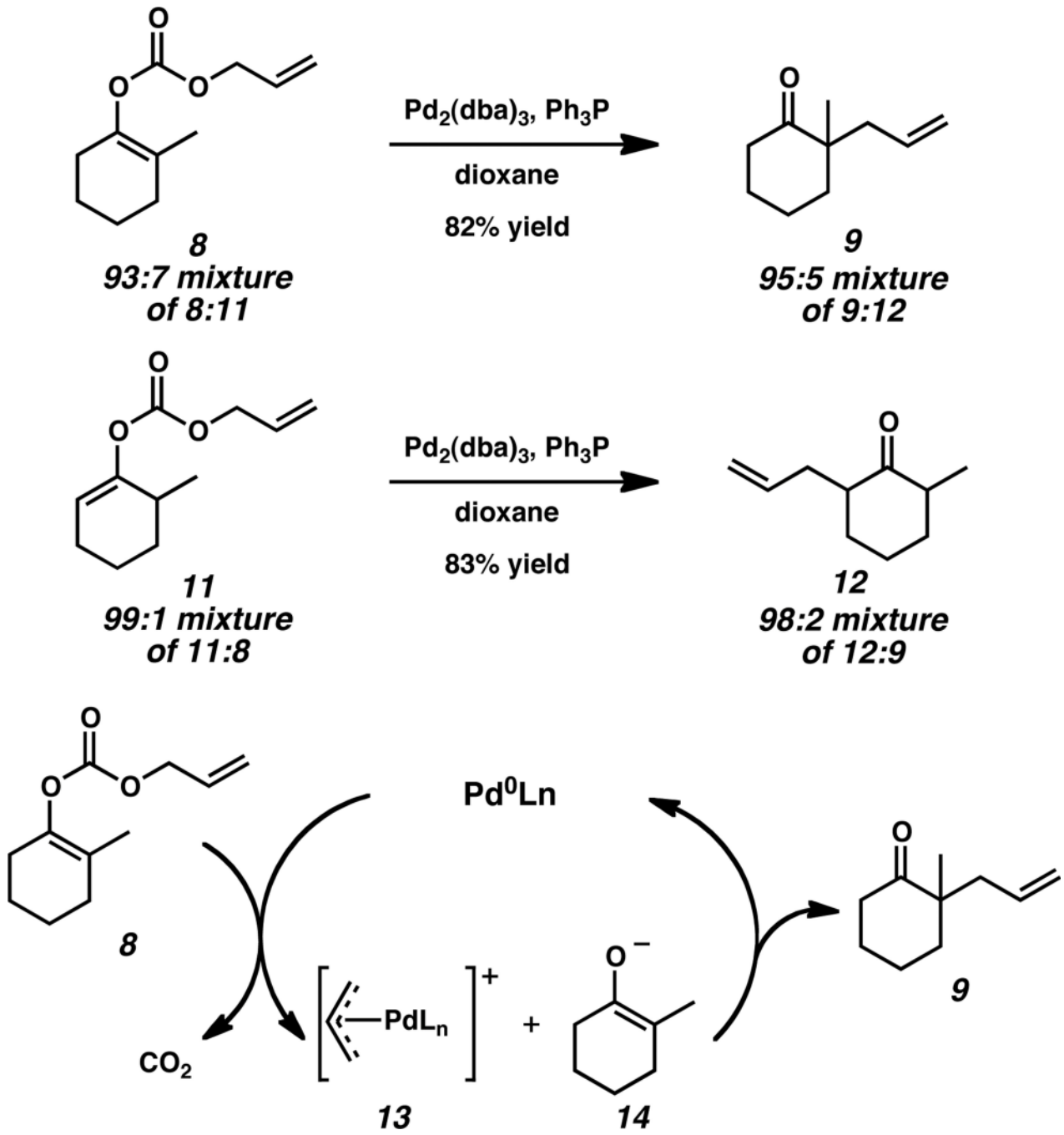
^{31}P NMR collected during the enantioselective allylation reaction: Spectrum A: (PHOX)Pd(dba) complex (18.8 ppm)[27d] and excess PHOX ligand (*S*)-**19** (−5.9 ppm) prior to addition of substrate; Spectrum B: After addition of substrate (±)-**10**, during reaction. Carboxylate **91** is observed at 30.9 ppm; Spectrum C: After complete consumption of substrate.



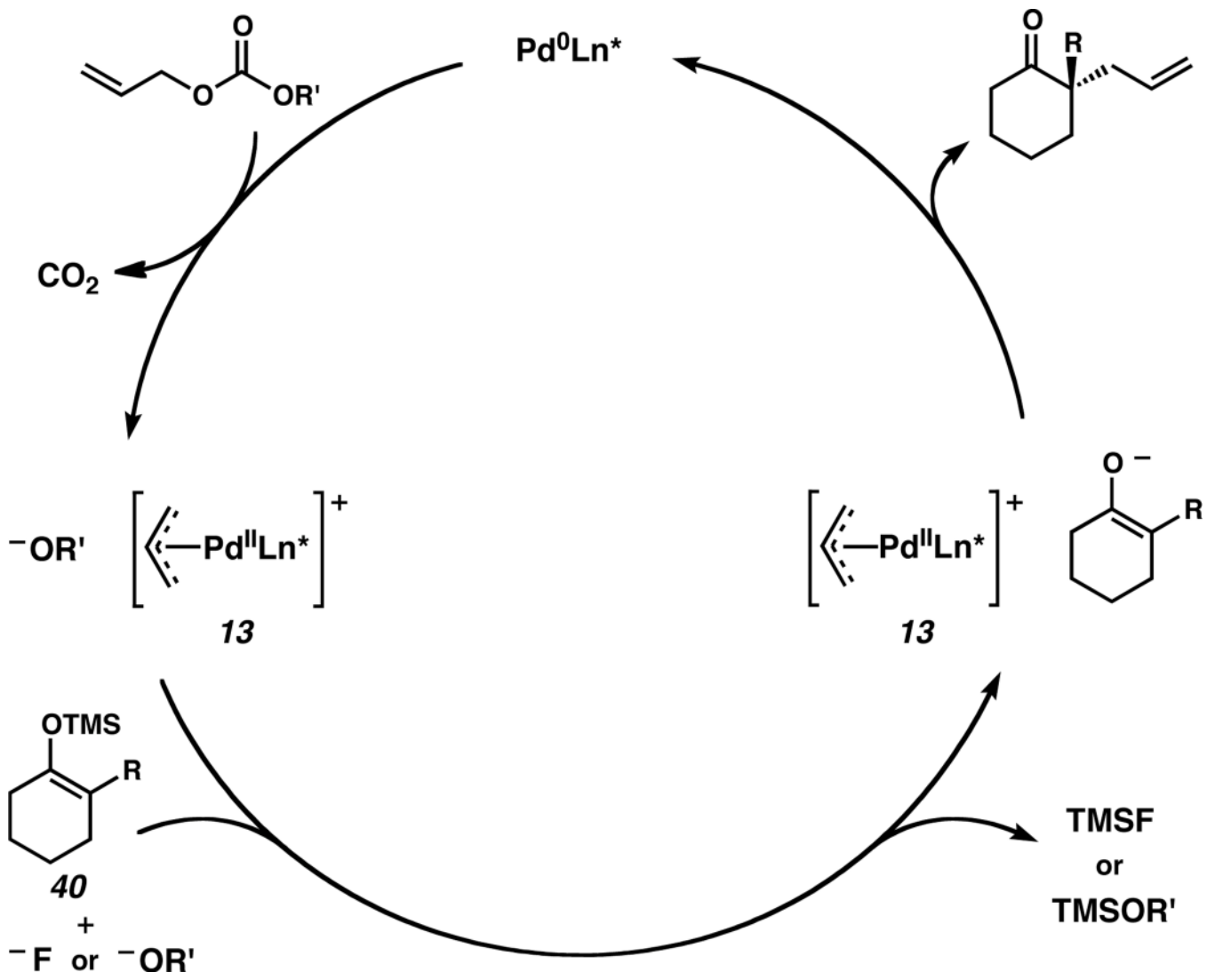
Scheme 1.
Trost's Allylic Alkylation with Prochiral Nucleophiles.



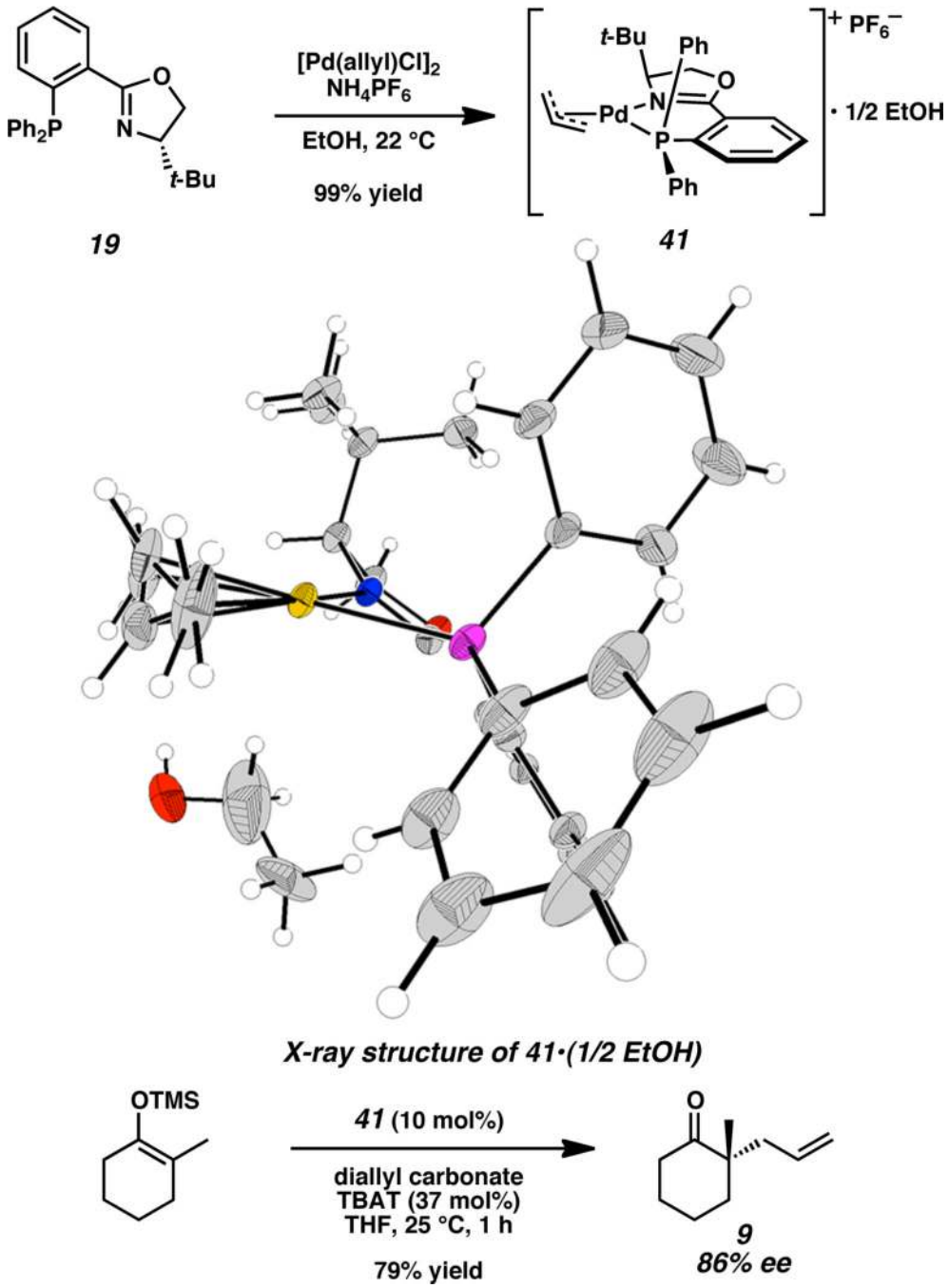
Scheme 2.
Tsuji's Allylation Methods.



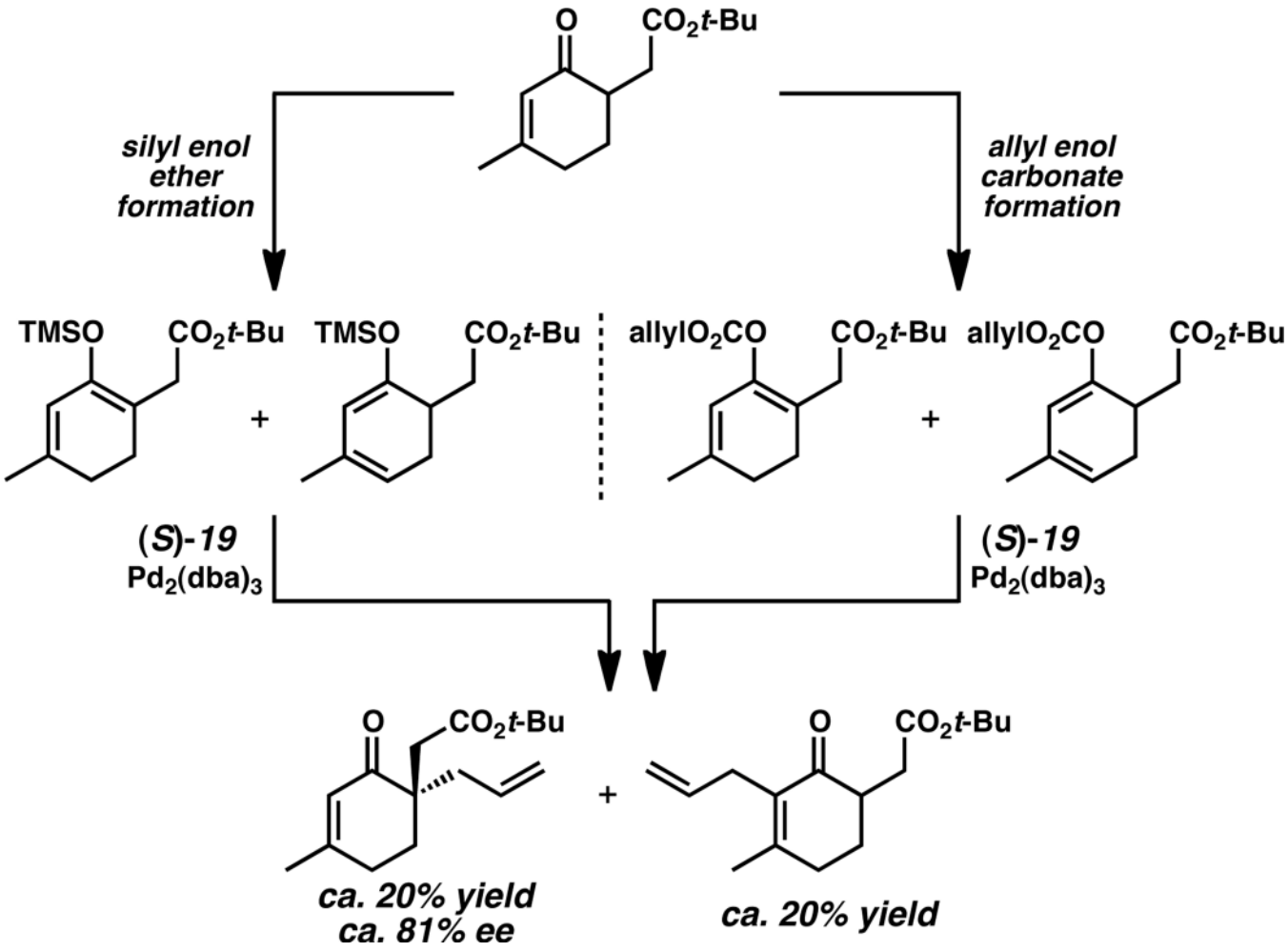
Scheme 3.
Regiochemical Fidelity in Tsuji's Palladium-Catalyzed Allylation.



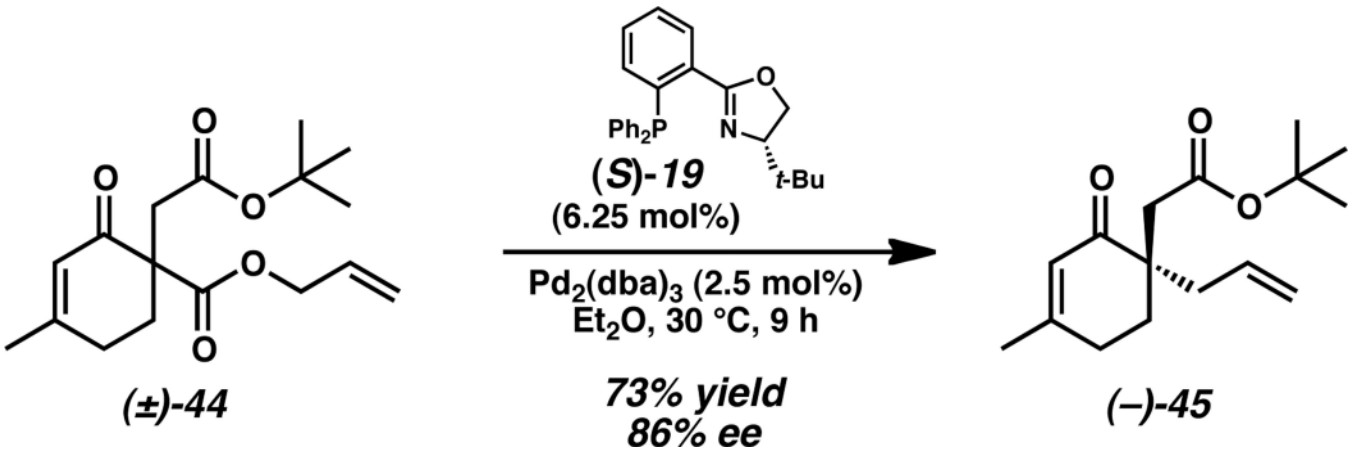
Scheme 4.
General Catalytic Cycle for Silyl Enol Ether Alkylation.



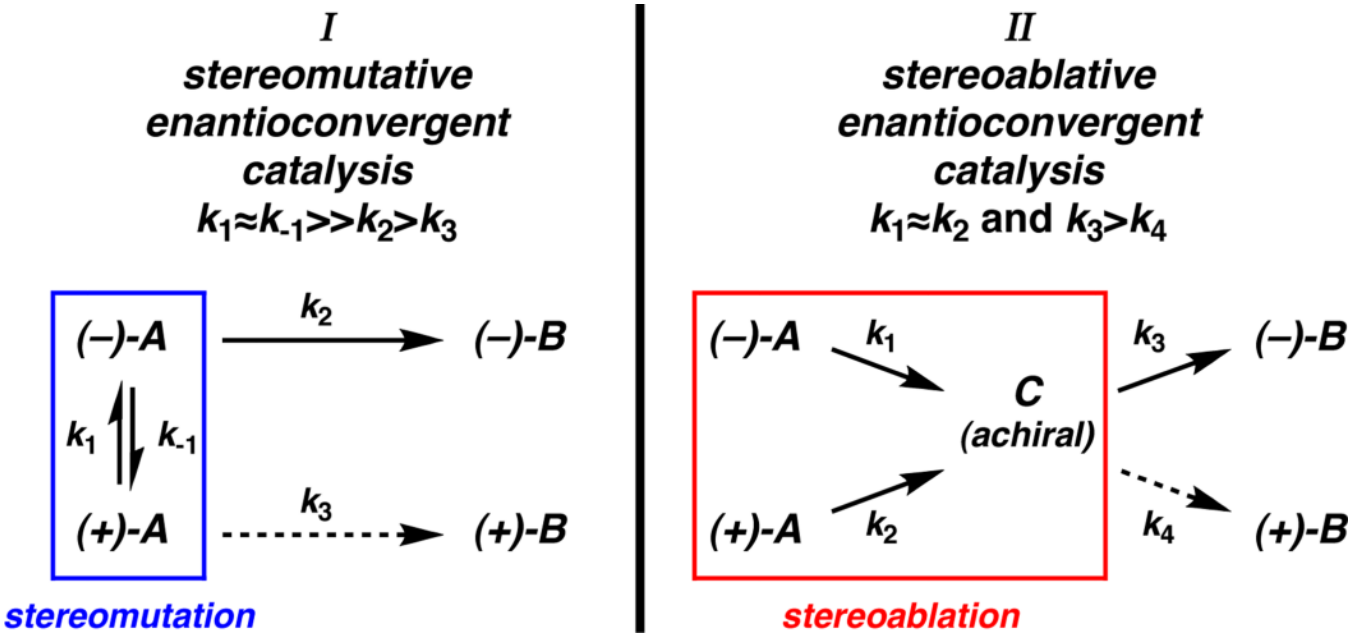
Scheme 5.
Allylation with Pd(II)PF_6 Salt **41**.



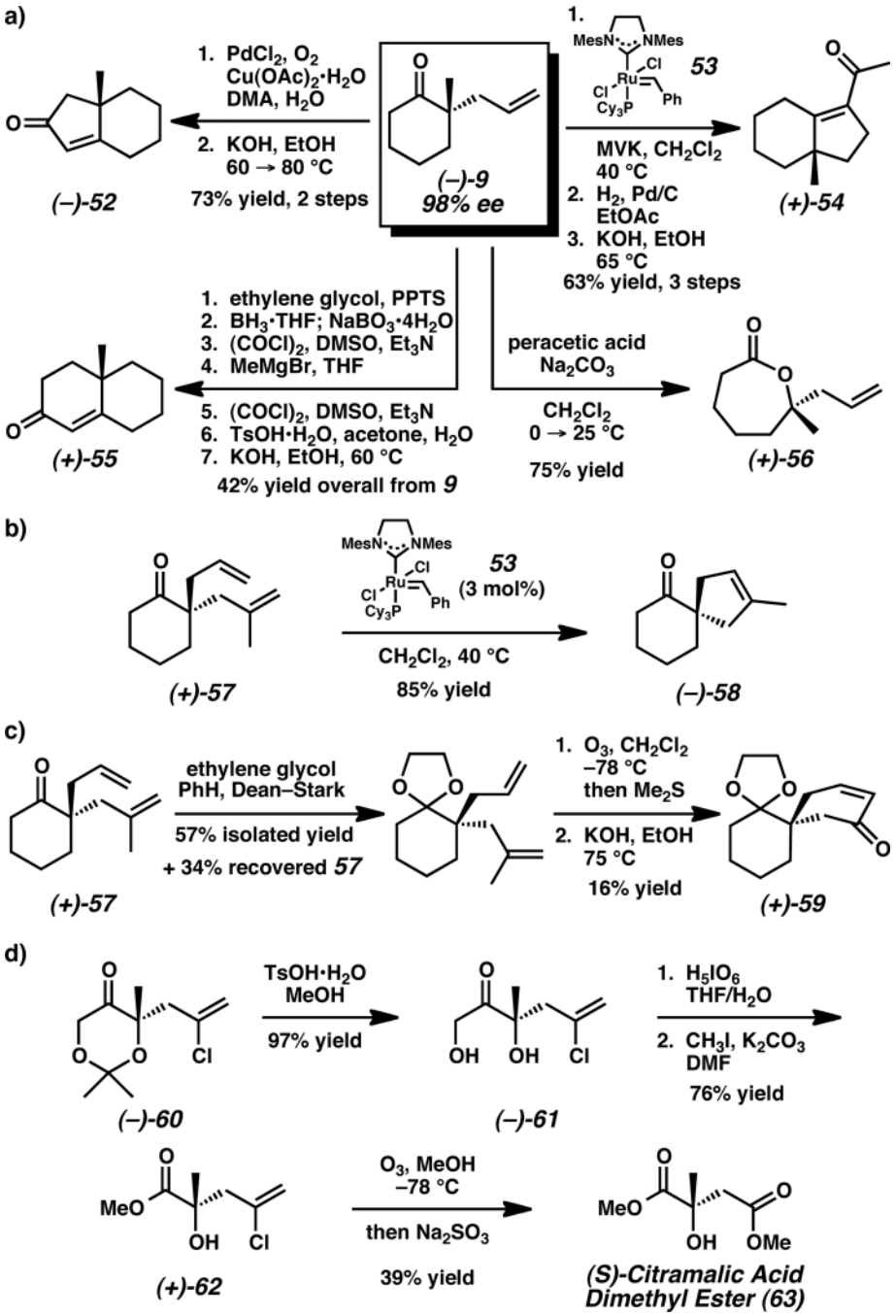
Scheme 6.
Non-selective Enolization Leads to Product Mixtures.



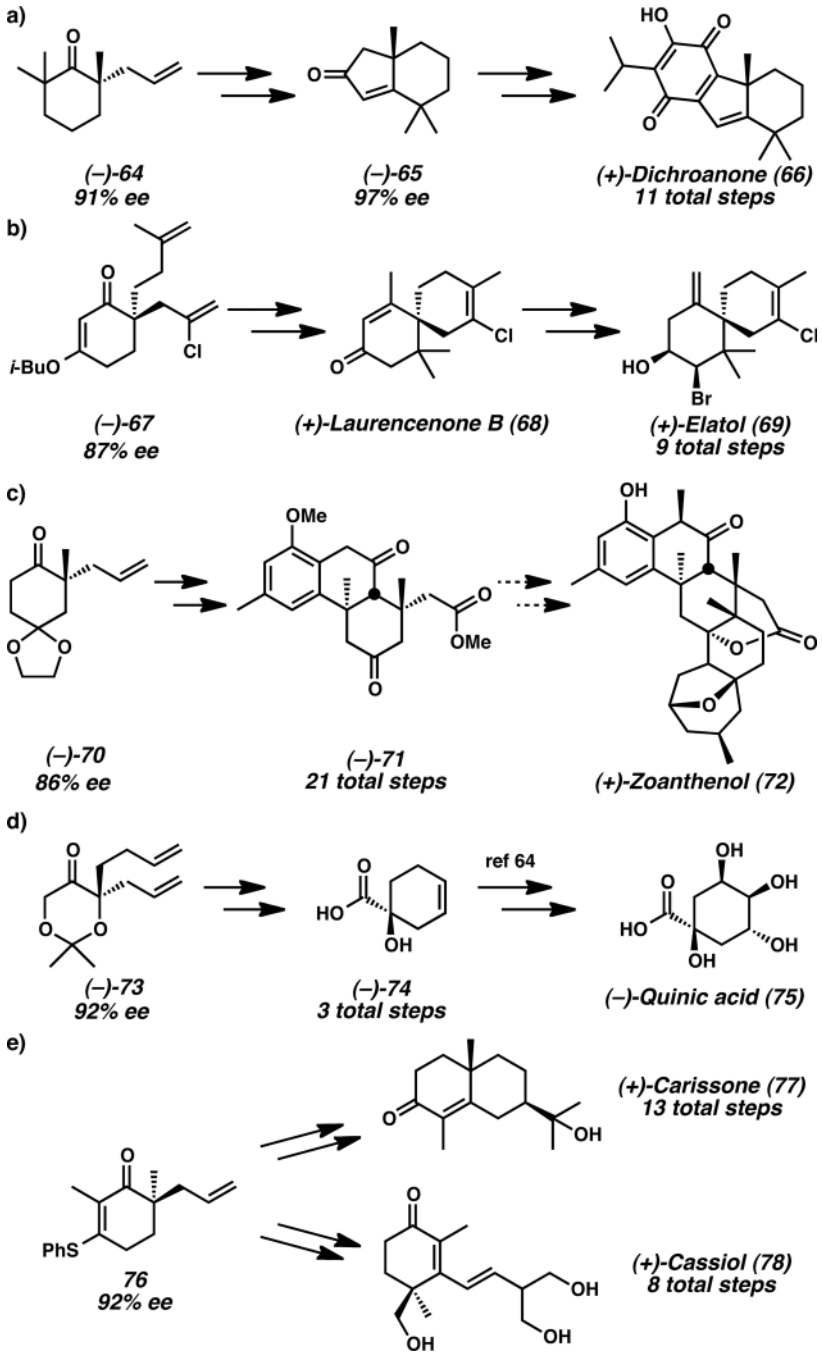
Scheme 7.
Enantioselective Decarboxylative Alkylation with an Allyl β-Ketoester.[27b].



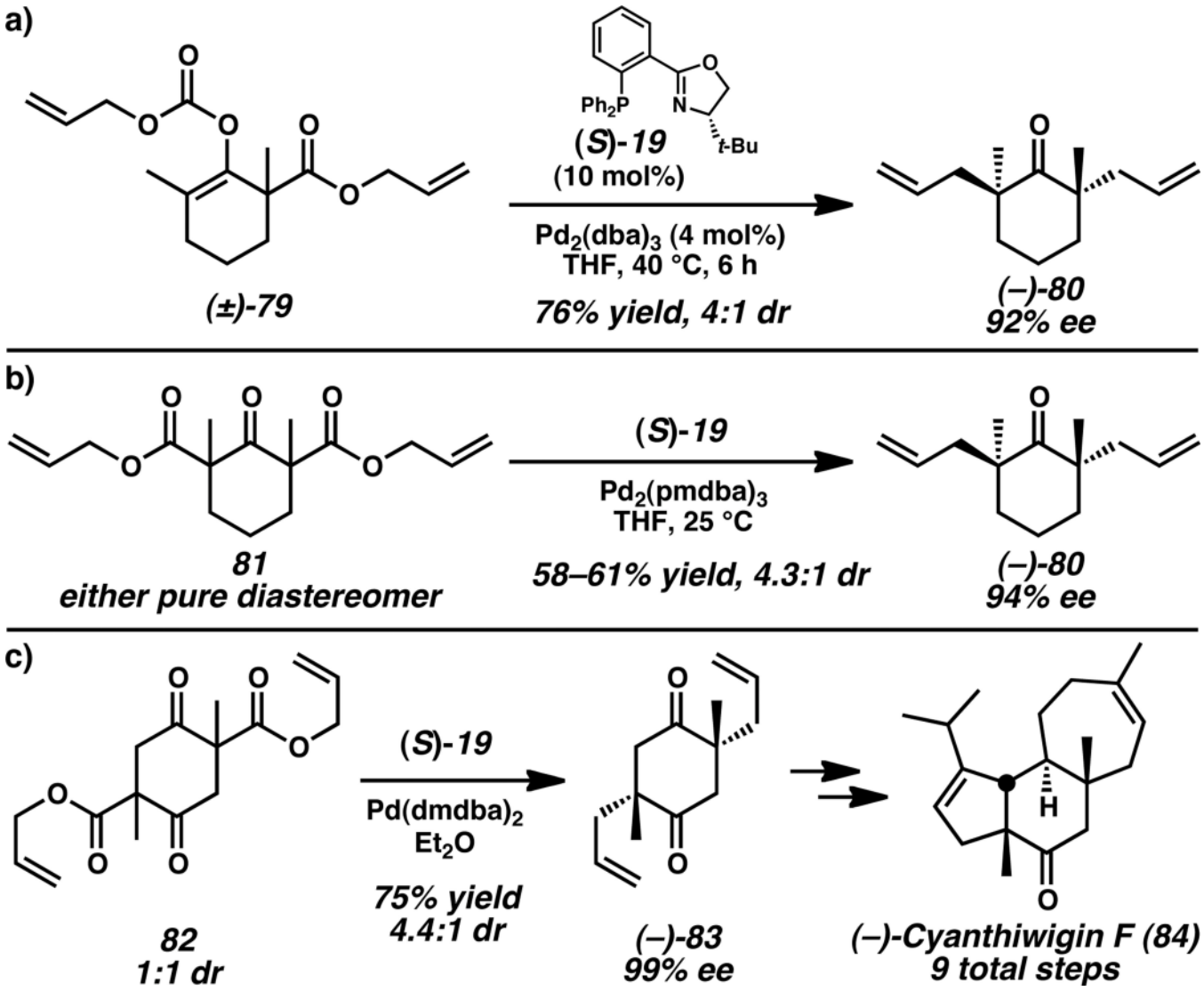
Scheme 8.
Stereoablative Enantioconvergent Catalysis.



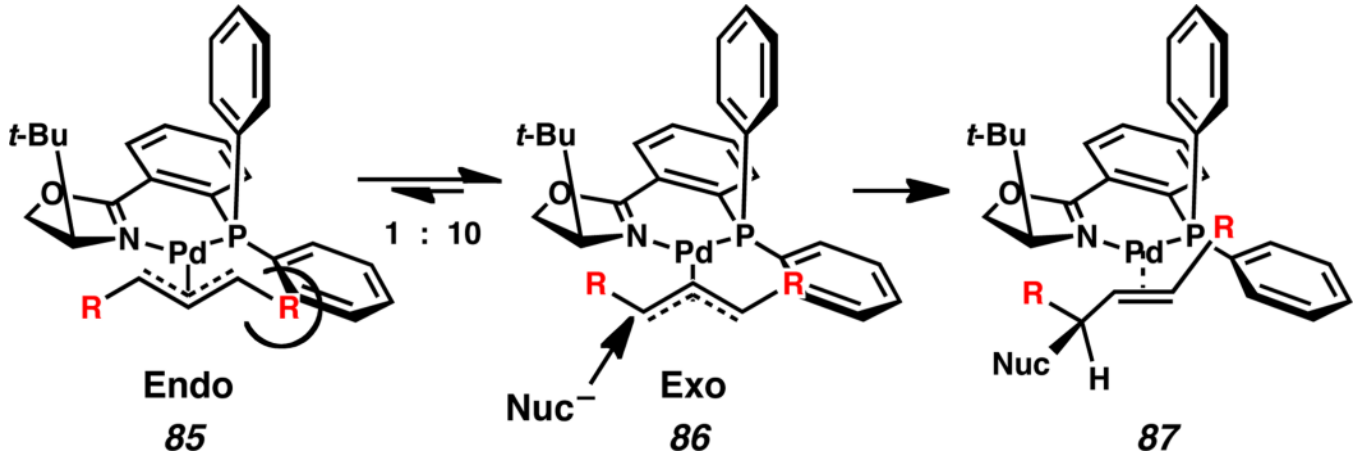
Scheme 9.
Useful Derivatives of Enantioenriched Cyclic Ketones.[27a,c]



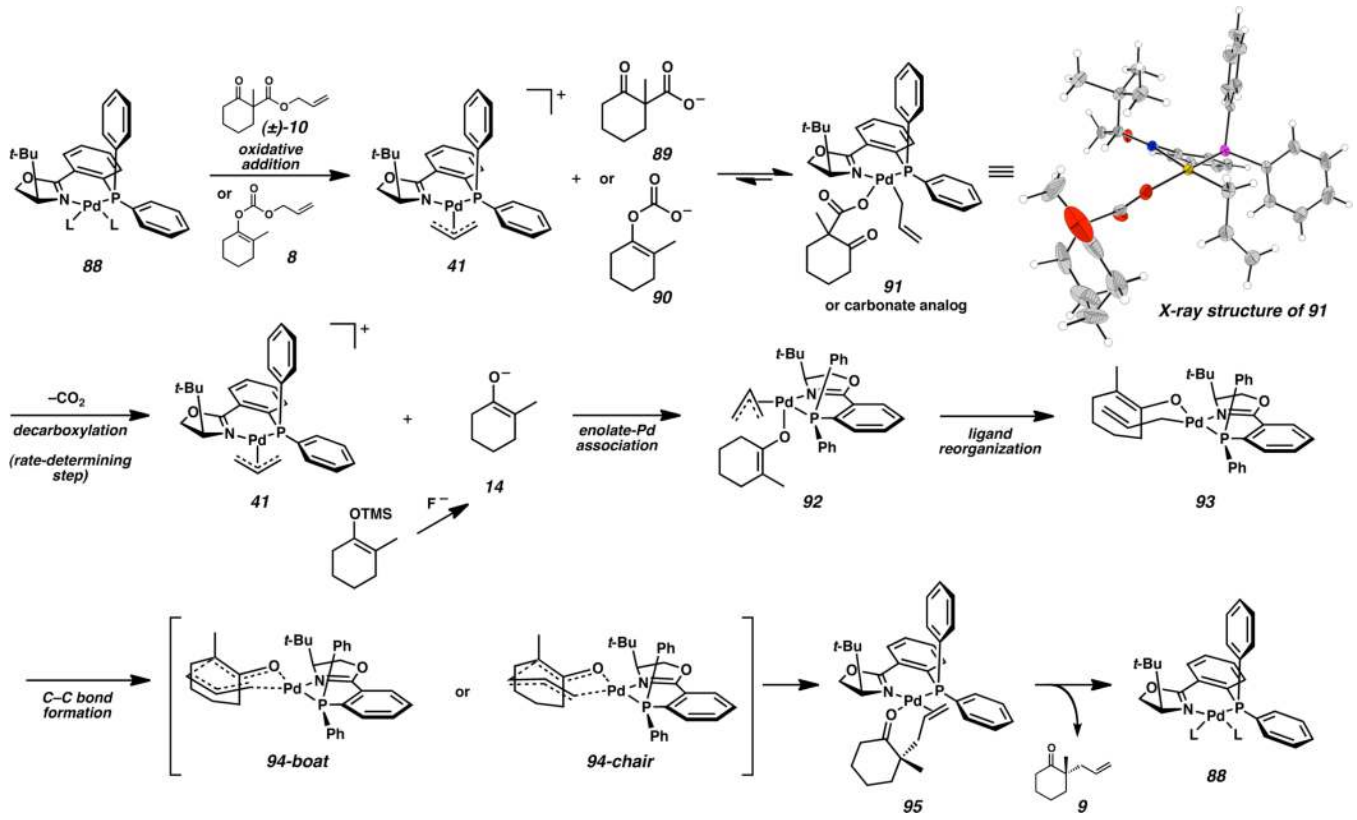
Scheme 10.
Enantioenriched Cyclic Ketones in the Synthesis of Natural Products.[24],[27c]



Scheme 11.
Enantioselective Cascade Allylations Generating Two Quaternary Centers.[27b,24d]

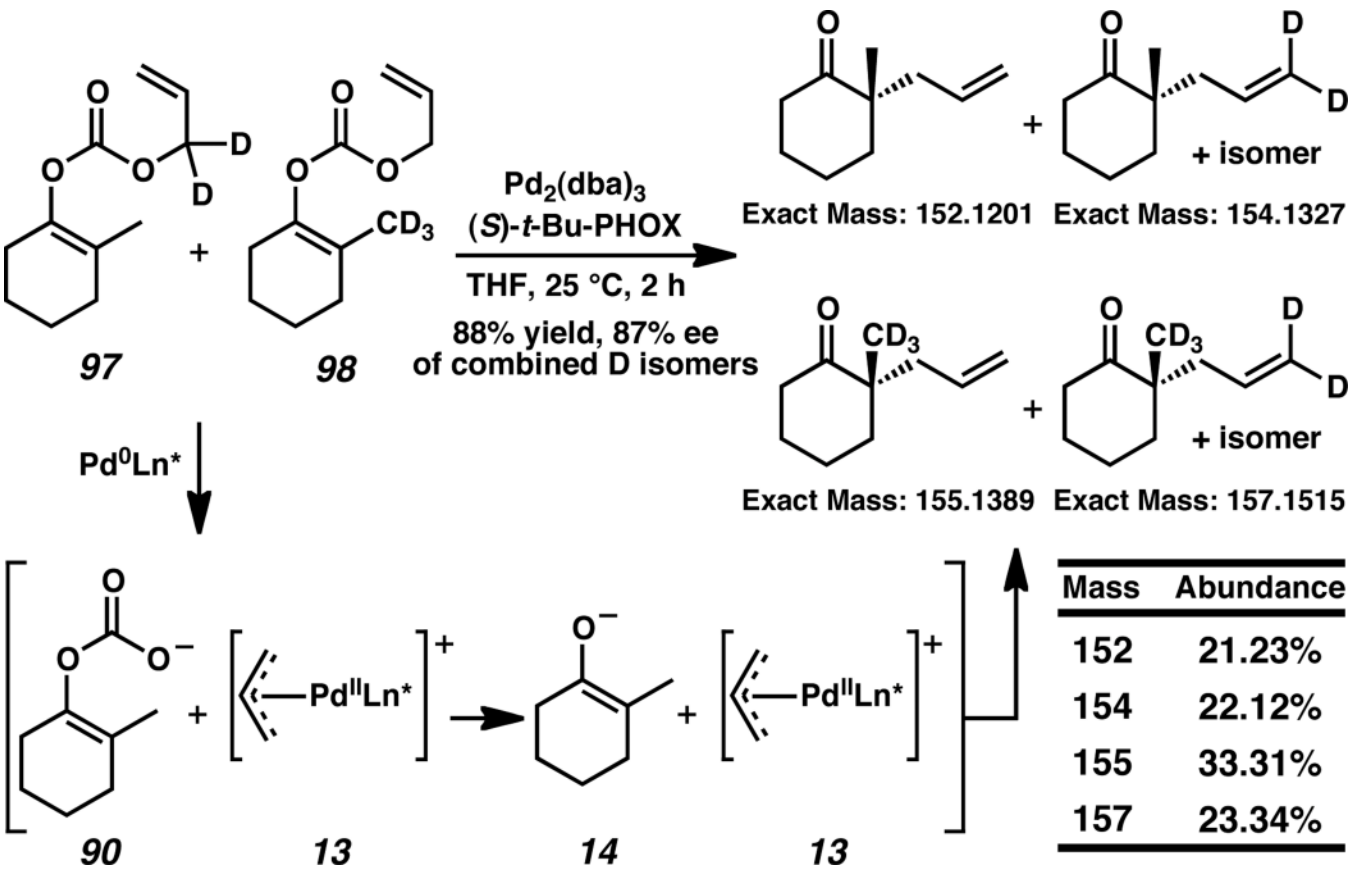


Scheme 12.
Helmchen's Outer-Sphere Mechanism for Asymmetric Allylation of Prochiral Allyl Electrophiles.



Scheme 13.

Proposed Inner-Sphere Mechanism for Asymmetric Alkylation of Prochiral Enolate Nucleophiles.



Scheme 14.
Crossover Experiments with Deuterated Allyl Enol Carbonates.[27b]

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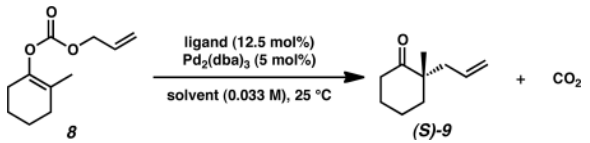
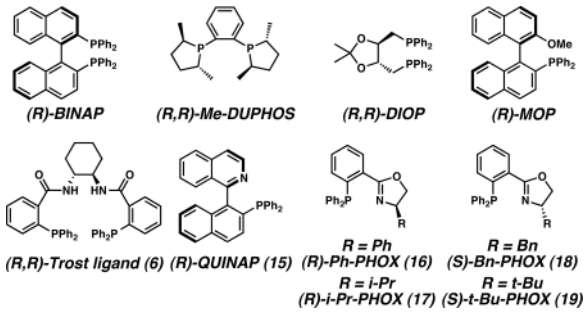
Table 1

Initial Ligand Screening.[27a]



		dioxane			THF		
entry	**ligand**	**time (h)**	**% yield[a]**	**% ee[b]**	**time (h)**	**% yield[a]**	**% ee[b]**
1	*(R)-BINAP*	5	92	5[c]	5	76	2[c]
2	*(R,R)-Me-DUPHOS*	5	61	0	5	66	0
3	*(R,R)-DIOP*	2	91	2[c]	2	59	2[c]
4	*(R)-MOP*	3	93	18	3	47	13
5	*(R,R)-Trost ligand (6)*	2	97	46[c]	5	92	64[c]
6	*(R)-QUINAP (15)*	2	98	61	2	97	61
7	*(R)-Ph-PHOX (16)*	2	95	62[c]	2	95	65[c]
8	*(S)-Bn-PHOX (17)*	3	96	65	5	94	63
9	*(R)-i-Pr-PHOX (18)*	3	96	82[c]	2	95	83[c]
10	*(S)-t-Bu-PHOX (19)*	2	95	86	2	96	88



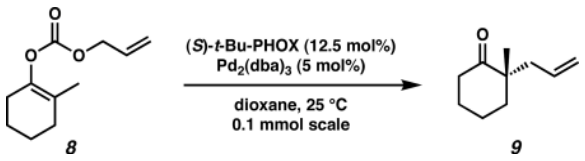
[a]GC yield of **9** relative to internal standard (tridecane).

[b]Enantiomeric excess by chiral GC.

[c] (*R*)-**9** produced as the major product.

Table 2

Effect of Concentration on Asymmetric Allylation.



entry[a]	concentration (M)	time (h)	% yield[b]	% ee[c]
1	0.500	3	81	82
2	0.250	2	90	84
3	0.125	2	94	84
4[d]	0.063	2	99	85
5	0.031	2	95	86

[a] Data reported are the average of three trials.

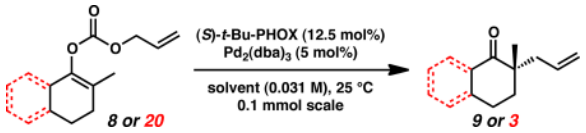
[b] GC yield relative to internal standard (tridecane).

[c] Enantiomeric excess measured by chiral GC.

[d] Data reported are the average of two trials.

Table 3

Effect of Solvent on Asymmetric Allylation.



		$9^{a,b}$			$3^{a,b}$	
entry	**solvent**	**time (h)**	**% yield[c]**	**% ee[d]**	**time (h)**	**% ee[e]**
1	dioxane	2	95	86	1	87
2	tetrahydrofuran	2	96	88	1	88
3	diethyl ether	2	98	89	1	80
4	*t*-butyl methyl ether	2	98	89	–	–
5	diisopropyl ether	2	95	89	–	–
6	anisole	3	82	81	–	–
7	1,2-dimethoxyethane	2	72	56	1	78
8	benzene	2	99	88	1	89
9	toluene	2	99	88	1	87
10	ethyl acetate	2	97	86	–	–
11	acetone	3	26	60	–	–
12	triethylamine	2	72	89	–	–
13	fluorobenzene	3	58	51	–	–
14	dichloromethane	3	42	13	–	–
15	chloroform	6	0	NA	–	–

[a] Data reported are the average of three trials.

[b] All reactions proceeded to complete conversion except entries 13–15.

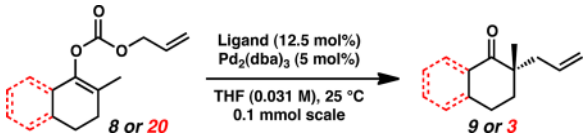
[c] GC yield relative to internal standard (tridecane).

[d] Enantiomeric excess measured by chiral GC.

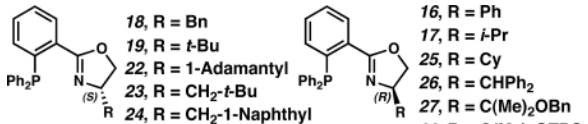
[e] Enantiomeric excess measured by chiral HPLC.

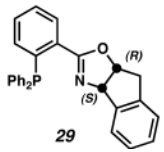
Table 4

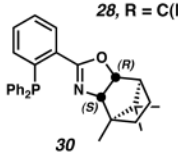
Effect of Phosphinooxazoline Sterics on Enantioselective Alkylation.



entry	ligand	product[a]	% ee[b]	entry	ligand	product[a]	% ee[b]
1	*16*	*9*	65 (*R*)	8	*25*	*9*	83 (*R*)
2	*17*	*9*	83 (*R*)	9	*26*	*9*	69 (*R*)
3	*18*	*9*	63 (*S*)	10	*27*	*3*	85 (*R*)
4	*19*	*9*	88 (*S*)	11	*28*	*3*	85 (*R*)
5[c]	*22*	*3*	78 (*S*)	12	*29*	*3*	79 (*S*)
6	*23*	*3*	59 (*S*)	13	*30*	*3*	81 (*S*)
7	*24*	*9*	41 (*S*)				







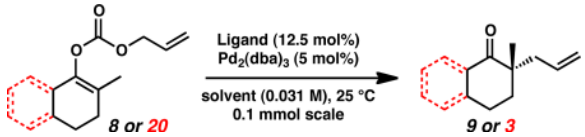
[a] All reactions proceeded to complete conversion.

[b] Enantiomeric excess measured by chiral HPLC or GC.

[c] Reaction run at 0.2 M in dioxane.

Table 5

Effect of Phosphine Electronics on Enantioselective Alkylation.



entry	product	ligand	solvent	% ee[b]	
1	*3*	*31*	dioxane	81	
2	*3*	*19*	dioxane	87	electron rich
3	*3*	*32*	dioxane	88	↓
4	*3*	*33*	dioxane	89	
5	*3*	*34*	dioxane	90	
6	*3*	*38*	dioxane	83	electron poor
7	*3*	*39*	dioxane	81	

entry	product	ligand	solvent	% yield[c]	% ee[d]	
8	*9*	*35*	THF	99	86	
9	*9*	*19*	THF	96	88	electron rich
10	*9*	*36*	THF	99	89	↓
11	*9*	*32*	THF	95	88	
12[e]	*9*	*33*	THF	97	87	
13[e]	*9*	*34*	THF	89	88	electron poor
14	*9*	*37*	THF	99	87	

entry	product	ligand	solvent	% yield[c]	% ee[d]
	31, R^1 = Me, R^2 = H				
	19, R^1 = H, R^2 = H				
	32, R^1 = F, R^2 = H				
	33, R^1 = CF_3, R^2 = H				
	37, Ar = *p*-$(CF_3)C_6H_4$				
	34, R^1 = H, R^2 = NO_2				
	35, R^1 = H, R^2 = OMe				
	36, R^1 = H, R^2 = CF_3				
	38, Ar = *m*-$(CF_3)_2C_6H_3$				
	39, Ar = C_6F_5				

[a] All reactions proceeded to complete conversion.

[b] Enantiomeric excess measured by chiral HPLC.

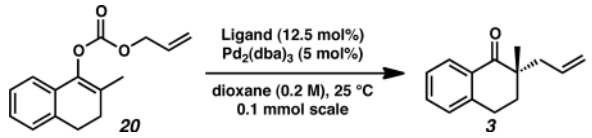
[c] GC yield relative to internal standard (tridecane).

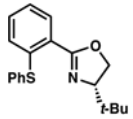
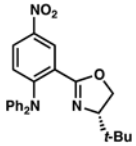
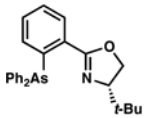
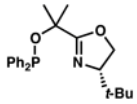
[d] Enantiomeric excess measured by chiral GC.

[e] Data reported are the average of two trials.

Table 6

Effect of Varied Heteroatom Chelates on Enantioselective Alkylation.



entry	ligand	% conversion	% ee[b]	entry	ligand	% conversion	% ee[b]
1		0[a]	ND	3		<5[a]	7
2		99[a]	52	4		87[c]	56

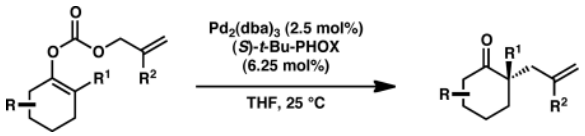
[a] Conversion estimated by TLC analysis.

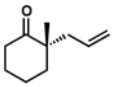
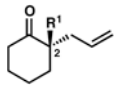
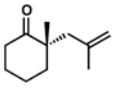
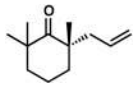
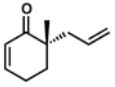
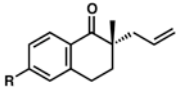
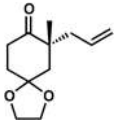
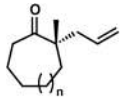
[b] Enantiomeric excess measured by chiral HPLC.

[c] Trial performed with allyl enol carbonate **8**. Conversion measured by GC relative to internal standard (tridecane). Enantiomeric excess measured by chiral GC.

Table 7

Substrate Scope for Asymmetric Allylation of Allyl Enol Carbonates.[27a]



entry	product[a]	% yield[b]	% ee[c]	entry	product[a]		% yield[b]	% ee[c]
1		85	87	7		$R^1 = CH_2CH_3$	96	92
2[d]		85	88 (96)[e]	8[g]		$R^1 = t$-Bu	55[h]	82
				9		$R^1 = CH_2Ph$	96	85
3[f]		90	89	10		$R^1 = (CH_2)_3OBn$	87	88
4[g]		89	91	11			94	92
5		91	89	12[i]		R = H	87	91
				13[i]		$R = OCH_3$	94	91
6		87	86	14		n = 1	81	87
				15		n = 2	90	79

[a]Reactions were performed using 1.0 mmol of substrate in THF (0.033 M in substrate) at 25 °C with 2.5 mol% $Pd_2(dba)_3$ and 6.25 mol% (*S*)-*t*Bu-PHOX (**19**), unless otherwise noted. Each reaction was complete in 1–10 h.

[b]Isolated yields.

[c]Measured by chiral GC or HPLC.

[d]Performed on 5.1 mmol scale.

[e]In parentheses is the % ee after one recrystallization of the corresponding semicarbazone.

[f]Reaction performed at 12 °C (GC yield).

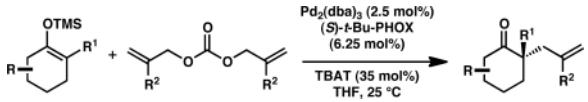
[g]Performed with 5 mol% $Pd_2(dba)_3$ and 12.5 mol% (*S*)-**19**.

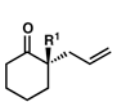
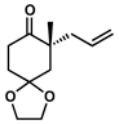
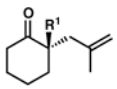
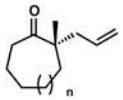
[h] Isolated yield after conversion to the corresponding diketone via Wacker oxidation.

[i] Performed at 10 °C.

Table 8

Substrate Scope for Asymmetric Allylation of Silyl Enol Ethers.[27a]



entry	product[a]		% yield[b]	% ee[c]	entry	product[a]		% yield[b]	% ee[c]
1		$R^1 = CH_3$	95	87	6			99	81
2		$R^1 = CH_2CH_3$	96	92					
3		$R^1 = OBn$	83	59					
4[d]		$R^1 = CH_3$	79	91	7		n = 1	94	86
5[d]		R^1 = allyl	82	91	8		n = 2	96	79

[a]Reactions were performed using 1.0 mmol of substrate in THF (0.033 M in substrate) at 25 °C with 2.5 mol% $Pd_2(dba)_3$, 6.25 mol% (*S*)-*t*Bu-PHOX (**19**), diallyl carbonate (1.05 equiv), and TBAT (35 mol%) unless otherwise noted. Each reaction was complete in 2–5 h.

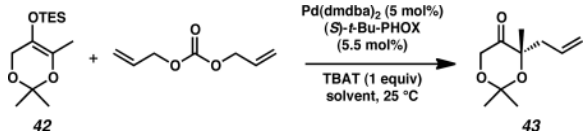
[b]Isolated yields.

[c]Measured by chiral GC or HPLC.

[d]Reaction performed with dimethallyl carbonate (1.05 equiv).

Table 9

Effect of Solvent in Dioxanone Alkylation.



42 43

entry	solvent	% yield[a]	% ee[b]
1	THF	40	81
2[c]	Et_2O	59	89
3	1,4-dioxane	65	67
4	benzene	67	84
5	toluene	74	88

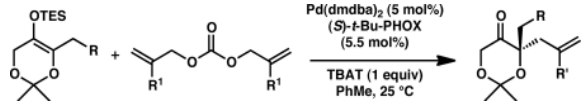
[a] Isolated yield from reaction using 0.1 mmol of substrate in solvent (0.033 M in substrate) at 25 °C with 5 mol% $Pd(dmdba)_2$, 5.5 mol% (*S*)-*t*Bu-PHOX (**19**), diallyl carbonate (1.05 equiv), and TBAT (1 equiv) unless otherwise noted. Each reaction was complete in 5–7 h.

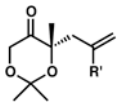
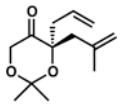
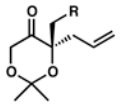
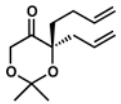
[b] Measured by chiral HPLC of a derivative.[53]

[c] Reaction performed at 30 °C.

Table 10

Enantioselective Alkylation Using Dioxanone Derived Enol Silanes.[27c]



entry	product[a]		% yield[b]	% ee[c]	entry	product[a]	% yield[b]	% ee[c]
1		R^1 = H	86	87				
2[d,e]		R^1 = CH_3	59	89	7		88	85
3[f]		R^1 = Cl	59	92	8[e]		93	88
4[g]		R^1 = Ph	73	94				
5		R = CH_3	79	93	9		83	92
6		R = Ph	85	86				

[a]Reactions were performed using 0.5 mmol of substrate in PhMe (0.033 M in substrate) at 25 °C with 5 mol% $Pd(dmdba)_2$, 5.5 mol% (*S*)-*t*Bu-PHOX (**19**), diallyl carbonate (1.05 equiv), and TBAT (1 equiv) unless otherwise noted. Each reaction was complete in 5–10 h.

[b]Isolated yields.

[c]Measured by chiral GC or HPLC, in some cases as a derivative.[53]

[d]Reaction performed with trimethyl silyl enol ether with 35 mol% TBAT in Et_2O (0.0167 M in substrate).

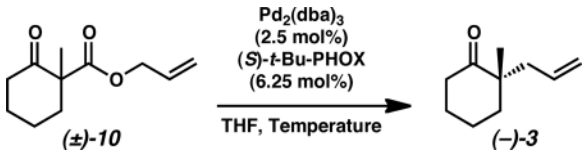
[e]Reaction performed with dimethallyl carbonate (1.05 equiv). The major product is enantiomeric to the structure shown.

[f]Reaction performed with dichloroallyl carbonate (1.05 equiv) at 35 °C.

[g]Reaction performed with diphenylallyl carbonate (1.05 equiv).

Table 11

Temperature Effects in Decarboxylative Allylation of Allyl β-Ketoesters.



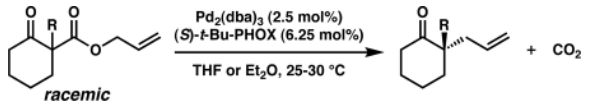
entry	temperature (°C)	time (h)	% yield[a]	% ee[b]
1	18	48	0	ND
2	25	7.5	85	88
3	30	2.25	82	87
4	35	1.25	85	86
5	40	0.67	86	85
6	60	0.15	82	83

[a] Isolated yield from reaction of 1.0 mmol substrate at 0.033 M.

[b] Determined by chiral GC.

Table 12

Enantioconvergent Decarboxylative Allylation of α-Substituted 2-Carboxyallylcyclohexanones.[27b]



entry	R	time (h)	yield[a]	ee[b]	entry	R	time (h)	yield[a]	ee[b]
1	CH_3	7.5	85	88	6	$CH_2C_6H_5$	0.5	99	85
2[c]	CH_3	4.75	89	88	7	$CH_2(4\text{-}CH_3OC_6H_4)$	10	80	86
3[c,d]	prenyl	6	97	91	8	$CH_2(4\text{-}CF_3C_6H_4)$	0.5	99	82
4[c]	CH_2CH_2CN	6.5	97	88	9[e]	$CH_2OTBDPS$	5	86	81
5[c,e]	$CH_2CH_2CO_2Et$	6	96	90	10[c,d]	F	3.5	80	91

[a] Isolated yield (%) from reaction of 1.0 mmol substrate with 2.5 mol% $Pd_2(dba)_3$ and 6.25 mol% (*S*)-*t*Bu-PHOX (**19**) at 0.033 M in THF at 25 °C, unless otherwise noted.

[b] Enantiomeric excess (%) determined by chiral GC or HPLC.

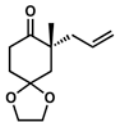
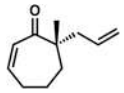
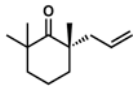
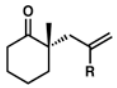
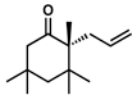
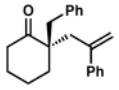
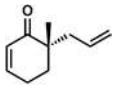
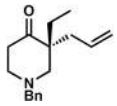
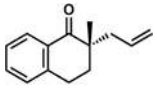
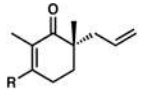
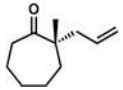
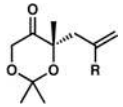
[c] Performed in Et_2O solvent.

[d] Performed at 30 °C.

[e] 4 mol% $Pd_2(dba)_3$, 10 mol% (*S*)-**19**, 0.021 M.

Table 13

Enantioconvergent Decarboxylative Allylation of β-Ketoesters with Substituted Carbocycles and Allyl Fragments.[24e,f,27a]

entry	product	% yield[a]	% ee[b]	entry	product		% yield[a]	% ee[b]
1		94	85	8[f]			98	90
2[c]		94	86					
3		89	90	9[d,e]		R = CH_3	87	92
				10[d,e]		R = Cl	87	91
4		90	85	11[g]			96	94
5[d,e]		77	90	12			91	92
6[d]		97	92	13[h]		R = *i*-BuO	86	75
				14[i]		R = PhS	85	92
7		83	87	15[d,j]		R = H	68	83
				16[d,j]		R = Cl	97	91

[a] Isolated yield from reaction of 1.0 mmol substrate, 2.5 mol% $Pd_2(dba)_3$ and 6.25 mol% (*S*)-*t*Bu-PHOX (**19**) at 0.033 M in THF at 25–35 °C, unless otherwise noted. Each reaction was complete in 1.5–12 h.

[b] Determined by chiral GC or HPLC.

[c] 25 mmol substrate, 1.5 mol% $Pd_2(dba)_3$, and 3.75 mol% (*S*)-**19**, 24 h reaction time.

[d] Performed in Et_2O.

[e] 4 mol% $Pd_2(dba)_3$, and 10 mol% (*S*)-**19** at 0.021 M.

[f] Reaction performed with 3.17 mmol substrate, 3 mol% $Pd(dmdba)_2$, and 3.8 mol% (*S*)-**19** at 0.060 M.

[g] 2.5 mol% $Pd(dmdba)_2$, 2.5 mol% (*S*)-**19**.

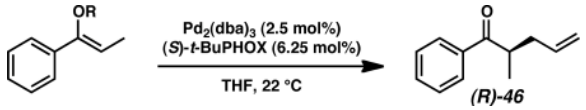
[h] Performed with 2.5 mol% $Pd_2(pmdba)_3$ and 6.25 mol% (*S*)-**19** in PhMe at 80 °C.

[i] Performed with 2.5 mol% $Pd_2(pmdba)_3$ and 6.25 mol% (*R*)-**19** in PhMe at 50 °C; major product was enantiomeric to the shown structure.

[j] 5 mol% $Pd(dmdba)_2$, 6.25 mol% (*S*)-**19**.

Table 14

Enantioselective Allylation of Allyl Enol Carbonates and Silyl Enol Ethers Not Contained in a Ring.



entry	R	additive	% yield[a]	% ee[b]	entry	R	additive	% yield[a]	% ee[b]
1	CO_2allyl	none	79	67	5[d]	TMS	CsF[f]	79	77
2	CO_2allyl	AgBr[c]	75	79	6[d]	TMS	CsF[f] AgBr[c]	20	79
3[d]	TMS	TBAT[e]	60	62					
4[d]	TBS	TBAT[e]	82	73	7[d,g]	TMS	CsF[f]	38	82

[a] Isolated yield from reactions with 0.092 mmol of substrate in THF (0.092 M) with 2.5 mol% $Pd_2(dba)_3$ and 6.25 mol% (*S*)-*t*Bu-PHOX (**19**), unless otherwise noted.

[b] Measured by chiral HPLC.

[c] 40 mol% additive.

[d] Reaction performed with diallyl carbonate (1.05 equiv).

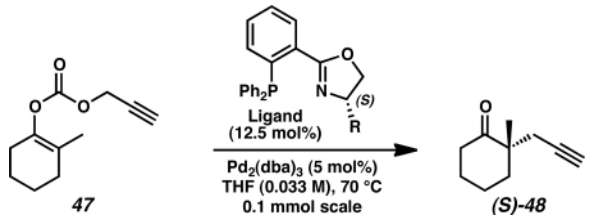
[e] 35 mol% additive.

[f] 48 mol% additive.

[g] Performed in Et_2O as solvent.

Table 15

Enantioselective Propargylation.



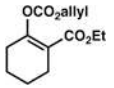
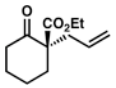
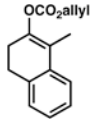
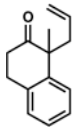
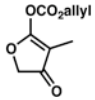
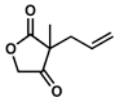
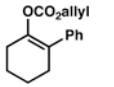
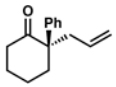
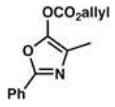
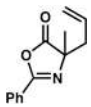
entry	ligand	% yield[a]	% ee[b]	entry	ligand	% yield[a]	% ee[b]
1	*19*, R = *t*-Bu	84	12	4	*24*, R = CH_2-1-Naphthyl	57	37
2	*23*, R = CH_2-*t*-Bu	83	32	5	*49*, R = CH_2-2-Naphthyl	71	26
				6	*50*, R = CH_2-(3,5-di-*t*-Bu-Ph)	94	25
3	*18*, R = CH_2Ph	54	26	7	*51*, R = CH_2-9-Anthracenyl	80	44

[a] GC yield relative to internal standard (tridecane).

[b] Enantiomeric excess measured by chiral GC. In all cases, (*S*)-**48** was the major enantiomer.

Table 16

Asymmetric Alkylation via Stabilized Allyl Enol Carbonates.[75]

entry	substrate	product	% yield[a]	% ee[b]	entry	substrate	product	% yield[a]	% ee[b]
1			89	24[c]	4			93	0
2			87	2					
3			99	11[c]	5			89	2

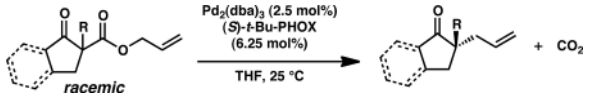
[a] Isolated yield from reactions with 1.0 mmol of substrate in THF (0.033 M) at 25 °C with 2.5 mol% $Pd_2(dba)_3$ and 6.25 mol% (*S*)-*t*Bu-PHOX (**19**). Each reaction was complete in 2 h.

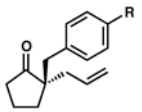
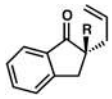
[b] Measured by chiral GC or HPLC.

[c] Absolute stereochemistry of products assigned by analogy.

Table 17

Enantioconvergent Decarboxylative Allylation of β-Ketoesters Containing Five-Membered Rings.



entry	product		yield[a]	ee[b]	entry	product		yield[a]	ee[b]
1		R = CH_2CH_3	82	86					
2		R = $CH(CH_3)_2$	77	84	6		R = OMe	84	73
3		R = CH_2NPhth	67	48	7		R = Me	84	73
4[c]		R = Me	82	80	8		R = CF_3	83	60
5		R = Bn	93	71					

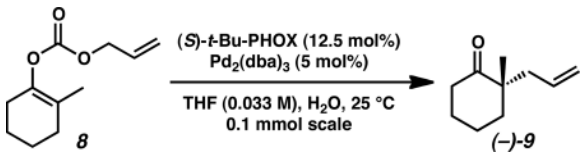
[a] Isolated yield (%) from reaction of 1.0 mmol of substrate in THF (0.033 M) with 2.5 mol% $Pd_2(dba)_3$ and 6.25 mol% (*S*)-*t*Bu-PHOX (**19**), unless otherwise noted. Each reaction was complete in 1–3 h.

[b] Enantiomeric excess (%) measured by chiral GC or HPLC.

[c] Performed on 0.1 mmol scale with 5 mol% $Pd_2(dba)_3$ and 12.5 mol% (*S*)-**19**.

Table 18

Effect of Water on Asymmetric Alkylation.



entry[a]	H_2O added (equiv)[b]	% yield[c]	% ee[d]
1	0	95	86
2	0.55	99	87
3	1.64	88	84
4	8.25	70	61
5	16.5	67	49
6	33.3	63	40

[a] Data reported are the average of three trials.

[b] H_2O added after Pd/PHOX complexation, but before substrate.

[c] GC yield relative to internal standard (tridecane).

[d] Enantiomeric excess measured by chiral GC.