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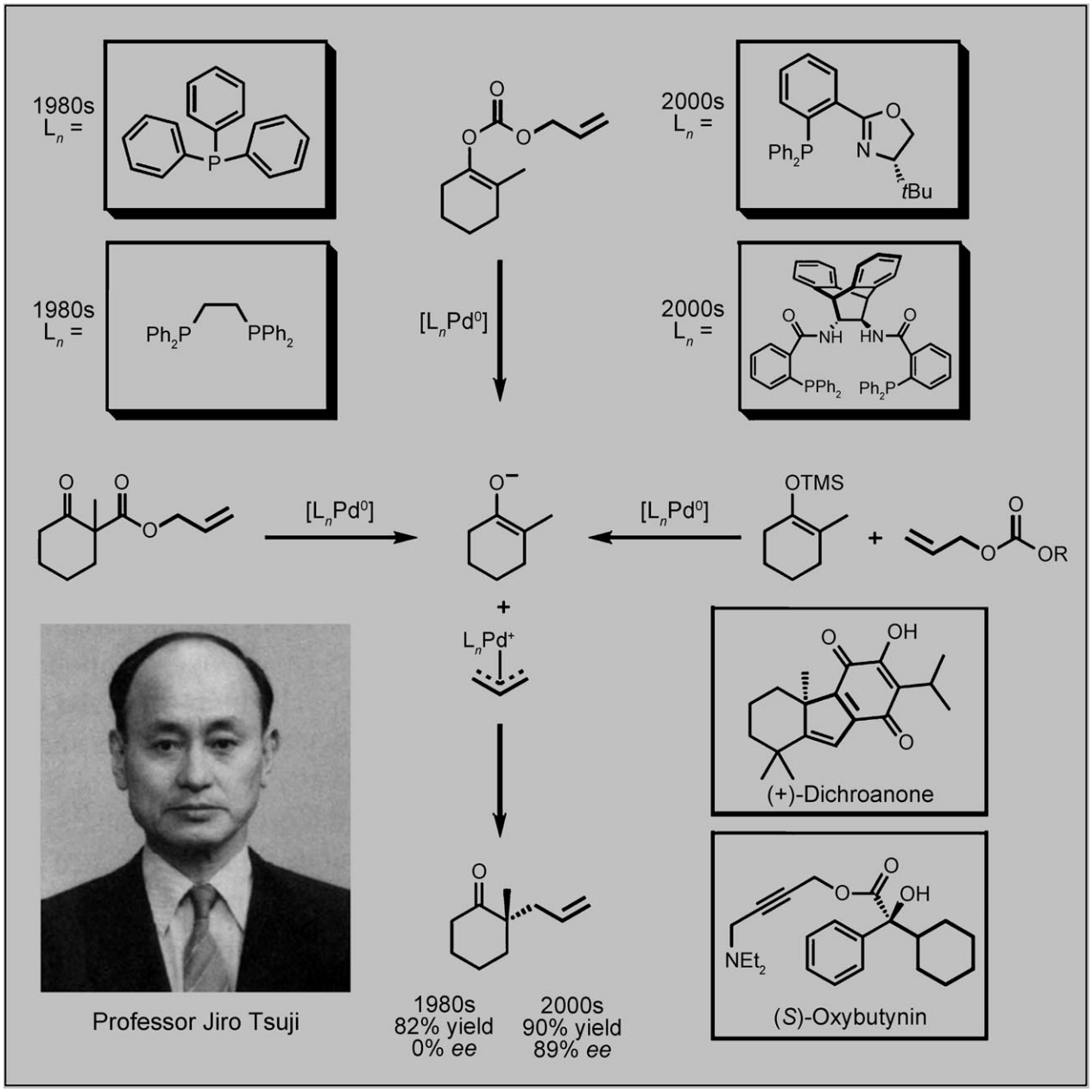
Enantioselective Tsuji Allylations

Justin T. Mohr and Brian M. Stoltz*[a]

Dedicated to Professor Jiro Tsuji on the occasion of his 80th birthday



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Abstract: The family of allylation reactions developed by Tsuji in the 1980s are capable of generating tertiary and quaternary carbon stereocenters from several synthetic precursors. Despite the utility of these transformations, they have seen little use in the synthesis of natural products. Recently, the power of these reactions was significantly enhanced by the development of enantioselective versions of these transformations. Applications of these methods to the enantioselective syntheses of natural products and pharmaceutical compounds highlight the importance of these developments.

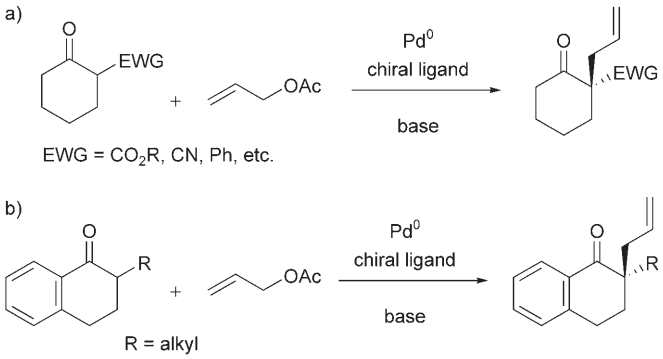
Keywords: allylation · asymmetric catalysis · enols · ketones · palladium

1. Introduction

1.1. Background and Significance

The catalytic enantioselective synthesis of quaternary carbon stereocenters is an ongoing challenge to synthetic chemists.[1] Any such reaction must forge a new carbon–carbon bond in the face of significant steric encumbrance to accomplish this goal. As a result, there are relatively few protocols that are both mild and highly enantioselective. Methods for the generation of quaternary stereocenters are extremely desirable given the prevalence of these stereogenic carbon centers in a wide variety of natural products with important structural and biological properties.

One important method for the enantioselective synthesis of quaternary stereocenters is the Pd-catalyzed allylic alkylation of prochiral stabilized enolates developed by Hayashi,[2] Ito,[3] Trost,[4] and Hou and Dai[5] and their co-workers (Scheme 1a). These reactions are unusual in the field of asymmetric allylic alkylation because the newly formed stereocenter resides on the nucleophilic partner instead of the electrophilic allyl group. Later, Trost[6] and Hou and Dai[7] and their co-workers described palladium-catalyzed systems capable of generating quaternary stereocenters with high enantiomeric excess from unstabilized ketone enolates that contain a single acidic position (e.g., tetralones; Scheme 1b).[8,9] Although these systems have proven useful in a number of applications, one limitation of this methodology is the requirement that there be only a single acidic site or a large pK_a difference between two acidic sites to prevent the formation of mixtures of allylated products from enolate scrambling in situ.[1b] As an example of this deficiency in the literature, the seemingly simple compound 2-allyl-2-methylcyclohexanone (**1**; Scheme 2) had not been prepared in highly enantioenriched form prior to the work discussed herein.[10]



Scheme 1. Enantioselective allylic alkylation with a) stabilized and b) unstabilized enolates.

1.2 History

In the 1980s, Prof. Jiro Tsuji[11] and his co-workers at the Tokyo Institute of Technology, and later at Okayama University, developed a series of Pd-catalyzed reactions in which unstabilized enolates or enol equivalents were transformed into the corresponding allylated ketones under essentially neutral reaction conditions. Viable substrates for these transformations included allyl enol carbonates,[12] silyl enol ethers,[13] allyl β-ketoesters,[14] and enol acetates[15] (Scheme 2). Importantly, each of these Pd-catalyzed decarboxylative reactions is capable of generating a quaternary carbon center.[16] Tsuji published several accounts of his work in the development of this suite of reactions.[17]

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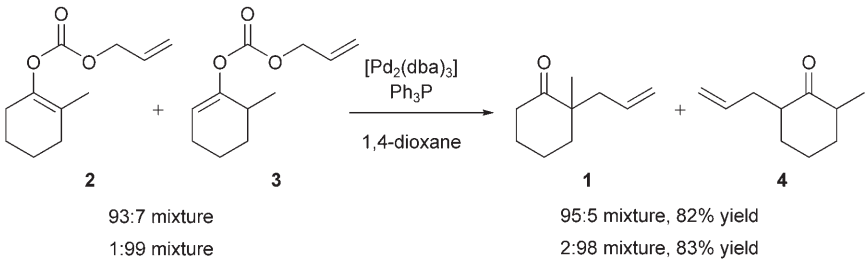
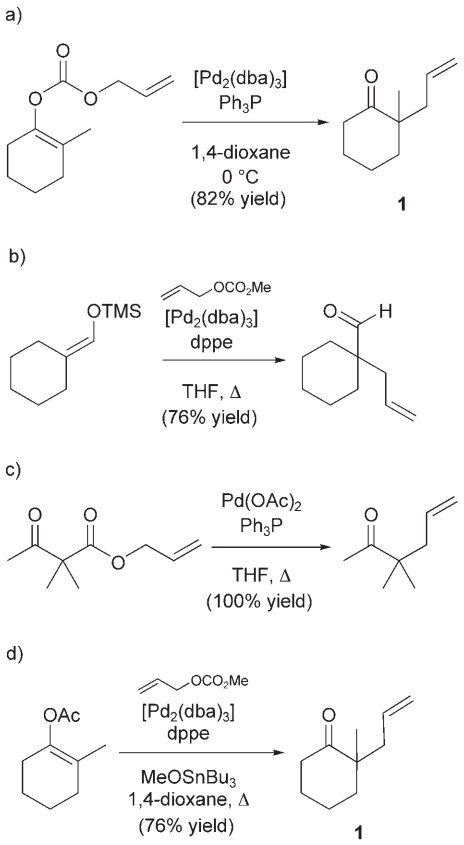
An important observation was the very high levels of regiochemical fidelity observed in these processes (Scheme 3). For example, a mixture of allyl enol carbonates enriched in tetrasubstituted enol isomer **2** was converted into α-quaternary ketone **1** with essentially no leakage of material to the isomeric ketone product **4**. Likewise, a mixture enriched in allyl enol carbonate **3** yielded ketone **4** with little trace of the α-quaternary isomer.[12] Despite this valuable quality, enantioselective variants of these transformations were not disclosed in the 20 years since the initial discoveries.



Scheme 3. Regiochemical fidelity in the Tsuji allylation.

Over the past three years, significant effort has been underway to develop enantioselective variants of the Tsuji reactions to address the limitations of the asymmetric allylic alkylation protocols. Viable methods for synthesizing all-carbon quaternary stereocenters adjacent to carbonyl groups have been reported from these investigations. In this Focus Review, the development and utility of these methods for the synthesis of complex molecules will be highlighted.[18] For the purposes herein, we define the Tsuji allylation as one of the four representative reactions detailed in Scheme 2. The enolate intermediate must be revealed in the course of the reaction with CO_2 as a by-product, the enolate



Scheme 2. Tsuji allylation reactions: a) allyl enol carbonates, b) silyl enol ethers, c) allyl β-ketoesters, and d) enol acetates. dba = dibenzylideneacetone, dppe = 1,2-bis(diphenylphosphanyl)ethane, TMS = trimethylsilyl.

Abstract in Japanese:

1980 年代に辻らによって見出された一連のアリル化反応は、非常に有用な 4 級炭素構築法といえる。しかしながら、その有用性にもかかわらず、これらのアリル化反応は一部の天然物合成に利用されただけであった。最近になって、これらのアリル化反応はエナンチオ選択的な反応へと展開し、その有用性は非常に高まった。中でも、エナンチオ選択的アリル化反応の天然有機化合物や医薬品化合物の不斉合成への応用は、本反応の有用性をより際立たせている。

Justin T. Mohr *was born in Anchorage, AK, USA in 1980. He received his AB in chemistry from Dartmouth College in 2003, where he worked in the laboratories of Prof. Gordon W. Gribble. He has been working toward a PhD with Prof. Brian M. Stoltz since 2003 as a Lilly Fellow, focusing on the development of enantioselective reactions of palladium enolates and their application to natural-product synthesis. His research interests include the development of carbon–carbon bond-forming reactions, enantioselective catalysis, and the synthesis of structurally and biologically interesting molecules.*

Brian M. Stoltz *was born in Philadelphia, PA, USA in 1970. After a year at Ludwig-Maximilians-Universität in München, Germany, he obtained his BS in chemistry and BA in German from Indiana Univ. of Pennsylvania in 1993. His PhD followed in 1997 under the direction of Prof. John L. Wood at Yale Univ. After an NIH postdoctoral fellowship with Prof. E. J. Corey at Harvard Univ. (1998–2000), he joined the faculty at Caltech in 2000 and is currently a Prof. of Chemistry. His research focuses on the synthesis of complex molecules with important biological properties and the development of new synthetic methods, including asymmetric catalysis and cascade processes.*

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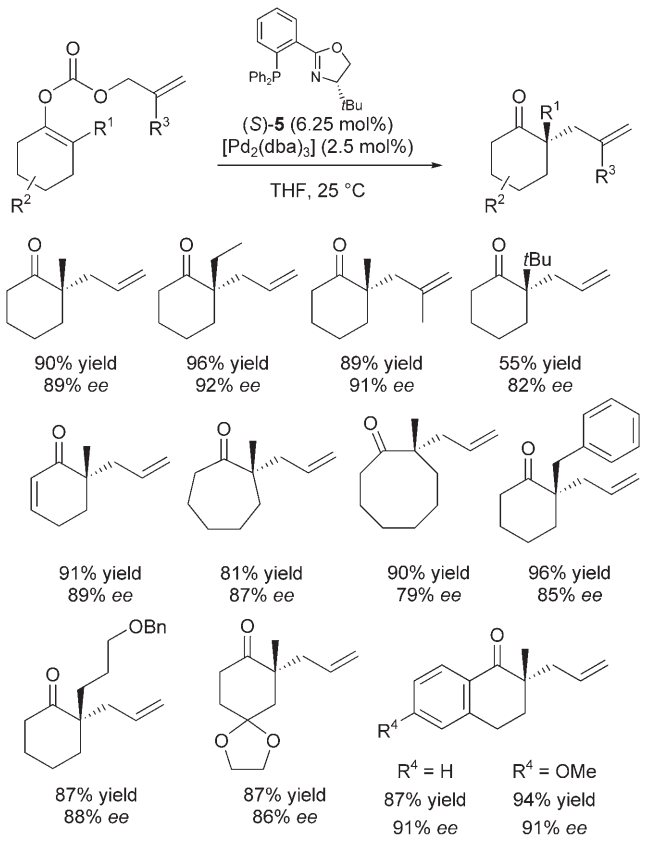
must be unstabilized by conjugated electron-withdrawing groups (e.g., esters), and the newly formed stereocenter must reside on the nucleophilic fragment of the product.

2. Allyl Enol Carbonates

2.1 Synthesis of Cyclic Ketones

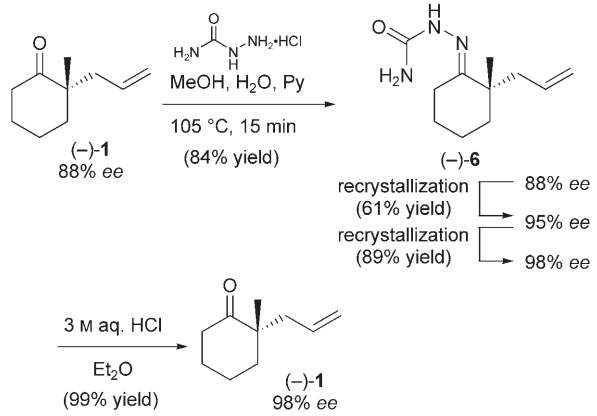
In 2004, our group reported an enantioselective Tsuji allylation from allyl enol carbonate substrates.[19] An initial screening of chiral ligands quickly identified that chelating P/N ligands were especially effective in terms of yield and enantioselectivity. Specifically, the *tert*-butyl phosphinooxazoline (*t*BuPHOX; **5**) ligand framework, developed in the 1990s by Pfaltz, Helmchen, and Williams,[20] led to the formation of the elusive 2-allyl-2-methylcyclohexanone (**1**) with up to 89% *ee*, the first reported synthesis of this simple enantioenriched ketone.

The extension of this result to more complex systems proved rewarding. The mild reaction conditions were tolerant of a variety of substituent and functional groups (Scheme 4). Remarkably, these adapted enantioselective Tsuji allylation conditions were capable of generating a quaternary stereocenter adjacent to another quaternary carbon atom in the formation of 2-allyl-2-*tert*-butylcyclohexanone with little degradation in enantioselectivity relative to less sterically demanding substrates. The absolute configuration was established for a number of products and, in all cases investigated, the enantiomer shown predominanted. An interesting effect observed in this work was that a range of solvents, including ethereal (THF, 1,4-dioxane, Et_2O, *tert*-butyl methyl ether, iPr_2O), aromatic (benzene, toluene), and carbonyl-containing (EtOAc) solvents, proved to be nearly equally effective for several substrates.



Scheme 4. Enantioenriched cycloalkanones produced from allyl enol carbonates. Bn = benzyl.

To improve the *ee* of the cycloalkanone products, a straightforward method of derivitization to the corresponding semicarbazone followed by recrystallization and hydrolysis was developed. This protocol allowed the isolation of **1** with 98% *ee* (Scheme 5).



Scheme 5. Enantioenrichment of ketone (−)-**1** via the semicarbazone derivative. Py = pyridine.

In 2005, Trost disclosed a similar system for enantioselective allylic alkylation from allyl enol carbonate substrates.[21] Although several P/P chelating ligands performed poorly in the work reported by our group,[19] Trost found that the uniquely shaped P/P ligand (*R*,*R*)-**7** provided high *ee* in the allylic alkylation of allyl enol carbonate substrates in toluene (Scheme 6). Two examples of substrates with multiple sites of similar acidity were reported. Interestingly, besides the enantioselective formation of quaternary centers, the use of trisubstituted enol precursors led to the formation of highly enantioenriched tertiary stereocenters. Further optimization of the reaction conditions was required in some cases to prevent multiple alkylations at the carbonyl α position of these trisubstituted enol precursors; use of 1,4-dioxane solvent effectively suppressed overalkylation for some substrates. Also included are the first examples of heterocycles in allylations of this type.[22]

An important facet of this chemistry is the observation that the major enantiomer of the cycloalkanone product is of the opposite sense to that observed in the earlier work of Trost's group with lithium–enolate nucleophiles and a similar ligand in the same enantiomeric series.[6a] This suggests that the mechanism of the reaction with preformed Li–enolate is significantly different from that with Pd–enolate generated in situ.

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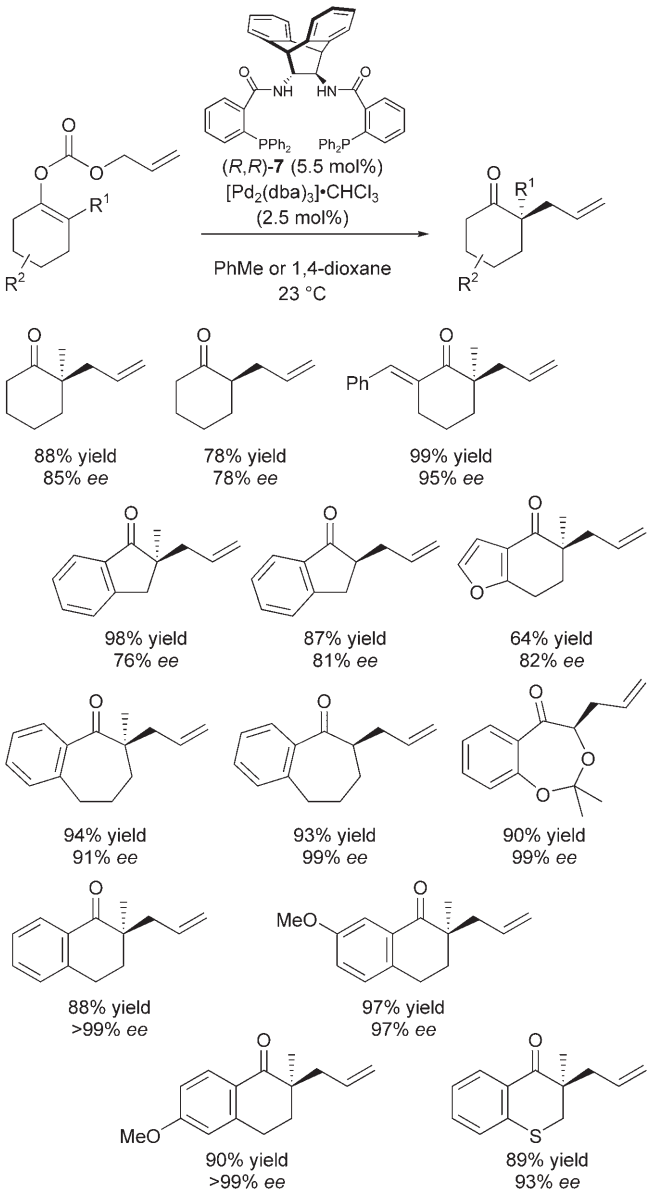
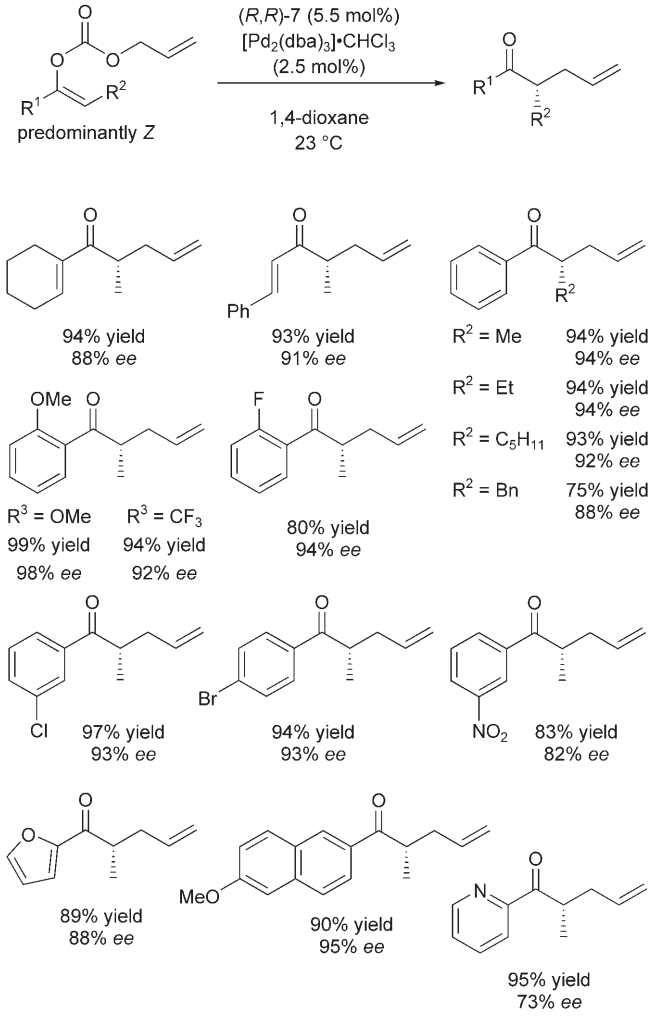


Scheme 6. Enantioenriched cycloalkanones produced from allyl enol carbonates.



Scheme 7. Enantioenriched ketones produced from *Z* enol carbonates.

2.2 Synthesis of Acyclic Ketones and Aldehydes

A significant advance in the development of these protocols is the extension to acyclic enolate precursors. Trost's group found that many α-tertiary ketones could be formed with high *ee* by using the (*R*,*R*)-**7**/Pd^0 catalyst system (Scheme 7).[23]

Interestingly, the geometry of the enol precursor affected not only the rate of reaction, but also the absolute configuration of the product (Scheme 8). This suggests that neither the enol carbonate nor the putative Pd–enolate complex undergoes significant geometric isomerization. No speculation regarding the origin of the large rate difference between enol isomers was given.

An extension of this chemistry was the incorporation of α-heteroatom-containing substrates. Trost et al. found that siloxy-substituted allyl enol carbonates are especially useful in this reaction and are particularly important because of the prevalence of α-hydroxyketones and aldehydes in natural products and pharmaceuticals.[22] Interestingly, isomeric substrates **8** and **10** each led to product **9**, which is derived from a probable aldehyde enolate intermediate (**12**; Scheme 9). This most likely occurred by an intramolecular silyl transfer between enolates **11** and **12** followed by subsequent allylation.

A variety of α-silyloxy aldehydes were prepared in this manner, including one cyclic example of an α-silyloxy ketone (Scheme 10). The isomer of the enolate precursor employed affected the rate of reaction and, to a small degree, the level of enantioselectivity. This rate difference was especially noticeable when substituted allyl fragments were employed. The *ee* of the major diastereomer formed in these cases was uniformly high, and the d.r. was typically high as well.

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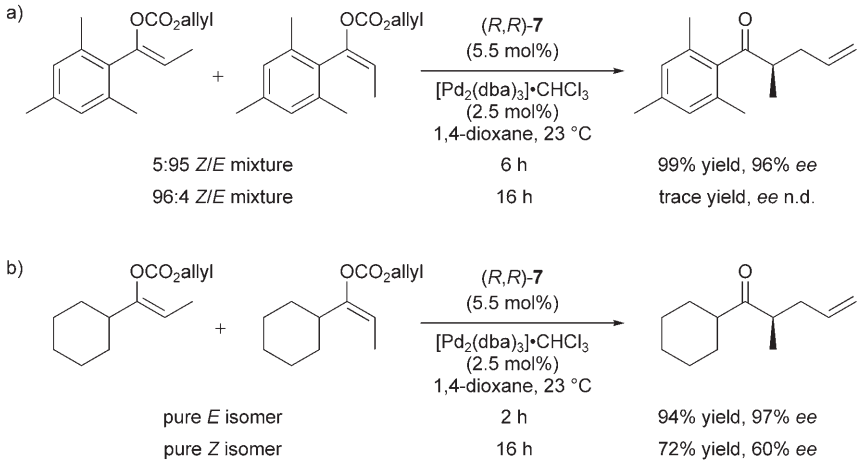
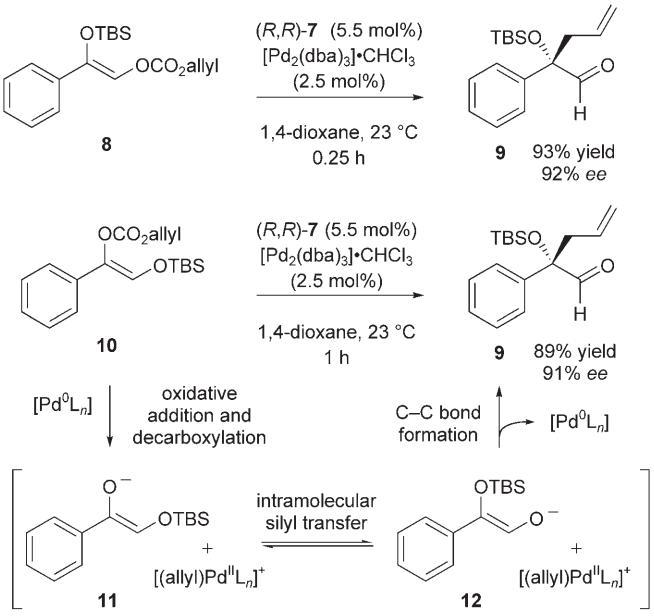


Scheme 8. Reactivity differences for *E* and *Z* enol carbonates. n.d. = not determined.



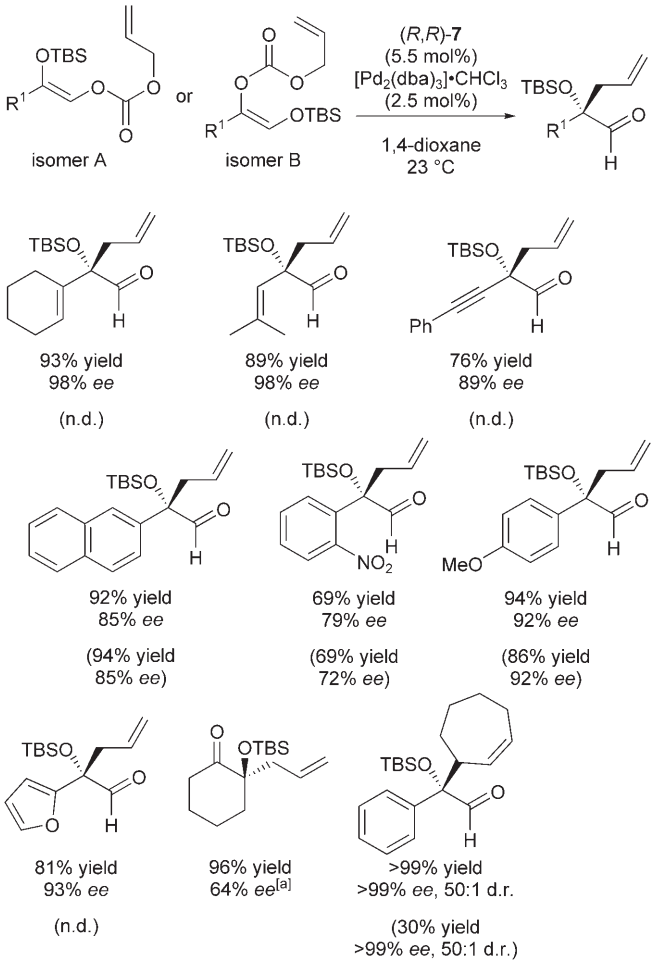
Scheme 9. Allylic alkylation from isomeric silyloxy-substituted allyl enol carbonates. TBS = *tert*-butyldimethylsilyl.

Allyl enol carbonate substrates provide the first entries to general allylation of ketone enolates. The importance of this class of enolate precursors is highlighted by their use in syntheses of natural products and pharmaceutical intermediates. Examples of these applications are discussed in Section 5.

3. Silyl Enol Ethers

Apart from allyl enol carbonate substrates, we demonstrated the application of the PHOX/Pd^0 catalyst system to a variety of silyl enol ethers.[19,24] These enol silanes are desirable enolate precursors because, in many cases, they are significantly easier to prepare than the corresponding allyl enol carbonates.

The intermolecular nature of this variant of the Tsuji allylation meant that the addition of a diallyl carbonate (**13**; Scheme 11) as a coupling partner was required. Although Tsuji et al. reported the allylation of silyl enol ethers without an exogenous activator,[13] it was found that the addition of a substoichiometric amount of the fluoride donor tetrabutylammonium difluorotriphenylsilicate (TBAT) was necessary for the enantioselective reaction at 25 °C. Notably, products obtained from allyl enol carbonate (Scheme 4) and silyl enol ether (Scheme 11) substrates had nearly identical *ee* with this catalyst system. This consistent enantioselectivity suggests that the mechanisms of C–C bond formation for both enolate precursors are identical.



Scheme 10. Allylic alkylation to form α-silyloxy aldehydes and ketones. Yields and *ee* values given are for isomer A (isomer B in parentheses). [a] Isomers A and B are identical.

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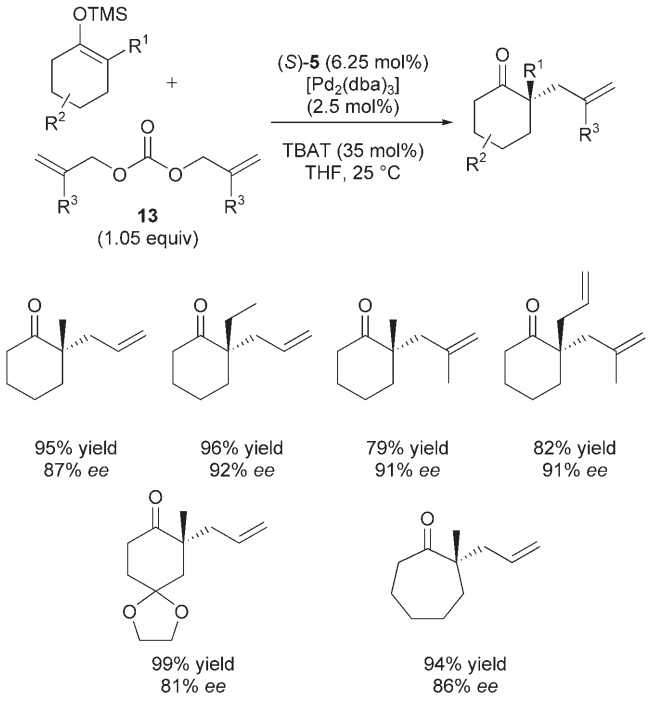
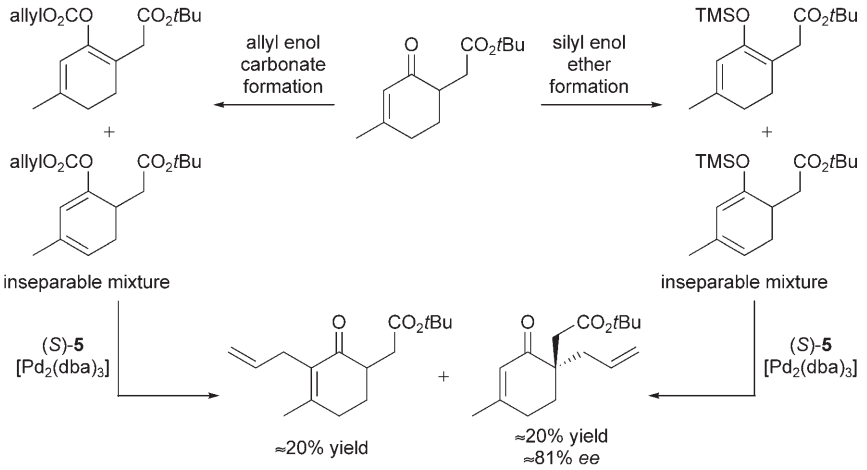


Scheme 11. Enantioenriched cycloalkanones produced from silyl enol ethers.

Although this class of substrate has not been developed to the extent of the allyl enol carbonate variant, the intermolecular reaction could be an important convergent coupling reaction of elaborate fragments toward complex target molecules. Furthermore, this method was recently used in the synthesis of stereodefined tertiary fluorides (see Section 5.4).



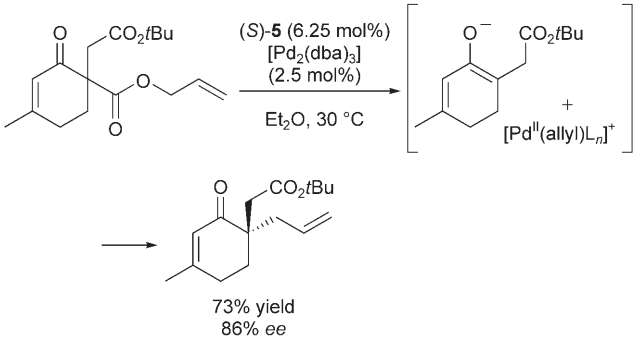
Scheme 12. Nonselective enolization leads to mixtures of allylated products.

4. Allyl β-Ketoesters

Although the above transformations have proven to be very useful, one particular shortcoming of these protocols is the need to pregenerate the enol equivalent prior to the allylation reaction with an exogenous base (typically an amine or amide base). In some cases, this enolization step provides poor selectivity for the desired enol isomer. Given the high level of regiochemical fidelity demonstrated by Tsuji (Scheme 3), these mixtures of enol isomers inevitably lead to mixtures of allylated products and, thus, poor yield. An example is shown in Scheme 12.

When confronted with this problem, our group found a possible solution in the work of Tsuji and Saegusa and their co-workers: allyl β-ketoesters, like the allyl enol carbonate substrates, contain all the necessary components for decarboxylative allylation, and the enolate generation is regiospecific.[14] However, the extension of this substrate class to enantioselective variants was potentially complicated by the intrinsic stereochemistry of the allyl β-ketoester, which could result in kinetic resolution or other problematic effects of double stereodifferentiation.[25] Despite that, substrate kinetic resolution was not observed, and the desired products were formed in excellent yield and with good *ee* (Scheme 13); this transformation of a racemic substrate into an enantioenriched product is an example of an enantioconvergent catalytic reaction.[26] The reaction probably proceeded through Pd-mediated oxidative addition and deallylation of the substrate followed by stereoablative C–C bond cleavage via decarboxylation to form an achiral enolate intermediate, then recombination of the fragments through Pd-mediated stereoselective C–C bond formation.

The substrate scope of the β-ketoester variant of the Tsuji allylation was found to be quite broad. Notably, compounds with high steric demands, such as 2-allyl-2,3,3,5,5-pentamethylcyclohexanone, were produced in good yield and with high *ee* (Scheme 14). Interestingly, substrates that bear β leaving groups did not suffer elimination, and substrates that contain other acidic functional groups (e.g., nitrile,



Scheme 13. Enantioselective decarboxylative allylation with an allyl β-ketoester.

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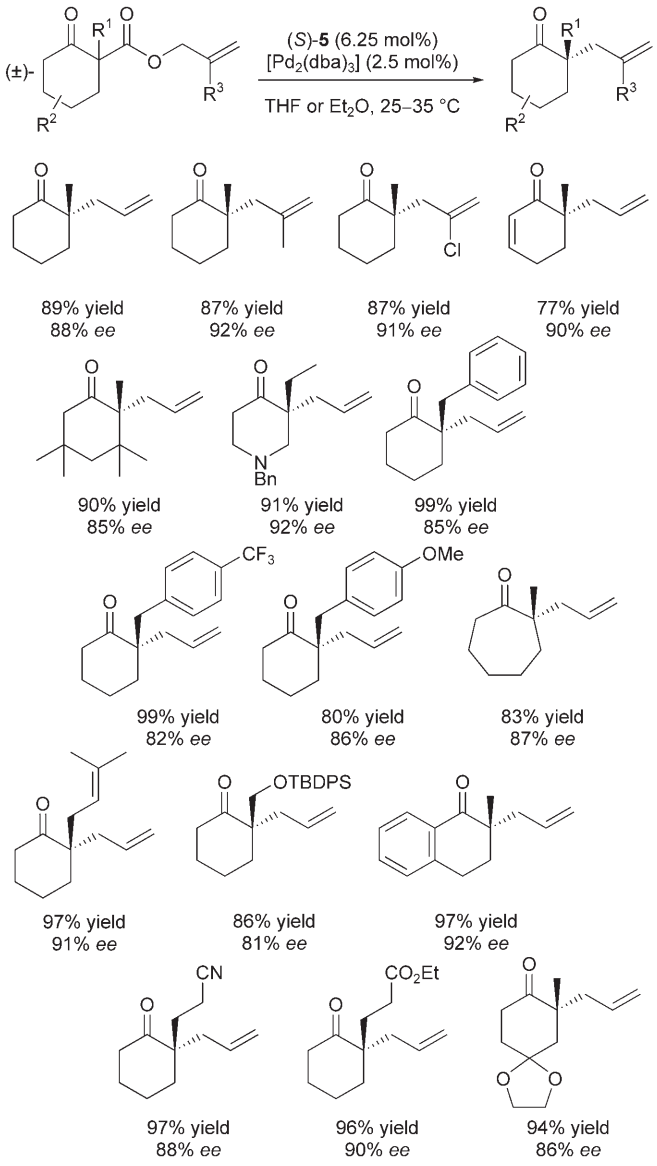
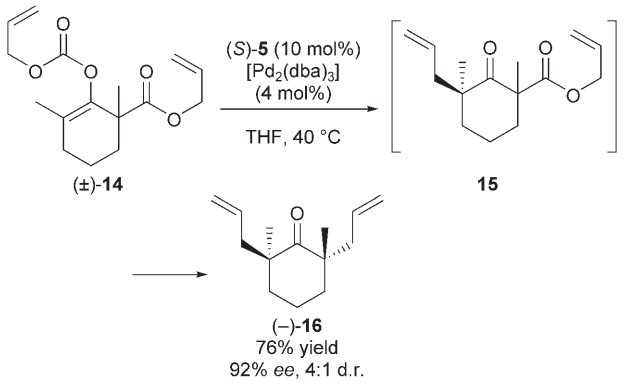


Scheme 14. Enantioenriched cycloalkanones prepared from allyl β-ketoesters. TBDPS = *tert*-butyldiphenylsilyl.

ester) did not cause enolate scrambling. Furthermore, allyl groups substituted at the central carbon atom (e.g., methyl, chloro) led to increased *ee*. The ketones produced from allyl β-ketoesters, allyl enol carbonates, and silyl enol ethers were formed in nearly identical yield and *ee* with this catalyst system.

Also demonstrated was the tolerance of a fluorine atom at the α position of the racemic substrate, a concept that was later developed further by Nakamura and others (see Section 5.4). In the work of Nakamura et al., three examples of the formation of quaternary stereocenters from allyl β-ketoesters were included as well.[27]

Apart from the development of the β-ketoester substrate class, we reported the use of a masked β-ketoester moiety to effect a cascade reaction that generates two quaternary stereocenters in a single reaction (Scheme 15).[26] Presumably, the allyl enol carbonate functionality of substrate **14** reacted rapidly, thus generating the first quaternary stereocenter and revealing allyl β-ketoester **15**, which underwent further reaction. Ketone **16** was isolated in 76% yield and with 92% *ee* as a 4:1 mixture of C_2/*meso* diastereomers.



Scheme 15. Enantioselective cascade allylation to generate two quaternary stereocenters.

Subsequent to this initial report, Trost et al. described the application of the bisphosphine/Pd^0 catalyst to the enantioselective allylic alkylation of vinylogous ester and thioester enolates.[28] When they were confronted with a similar problem of nonselective enolization in enol carbonate formation, the β-ketoester motif was explored. Unlike the PHOX system, some variation in product *ee* was observed, depending on the nature of the enolate precursor (i.e., allyl enol carbonate vs. allyl β-ketoester). Notably, the level of substrate conversion observed was sensitive to the nature of the substituent of the vinylogous ester moiety. To address this problem, vinylogous thioester substrates were examined, and the reactivity was improved. A variety of substitutions were possible, and products with high *ee* were obtained in many cases (Scheme 16). Details of the synthetic utility of these products are shown in Section 5.6.

Trost et al. suggested that substrates that bear Lewis basic groups (e.g., alkyne or carbonyl) nearby may cause a decrease in enantioselectivity by chelating to palladium in the course of enantiodetermination, thereby leading to decreased *ee* in the product. This effect contrasts results in our work, whereby neighboring Lewis basic groups had little effect (Scheme 14).

Allylation in the presence of an acidic 1,3-diester moiety highlighted the regiochemical fidelity of the allylation process in an extreme case, although the *ee* was decreased considerably (Scheme 17).

Allyl β-ketoester substrates are very practical because of the simple substrate preparation, the bench-top stability of quaternary β-ketoesters, and the relative ease of purification. The enantioconvergent nature of this reaction is conceptually interesting and provides a useful method for the conversion of racemic materials into valuable enantioenriched products.

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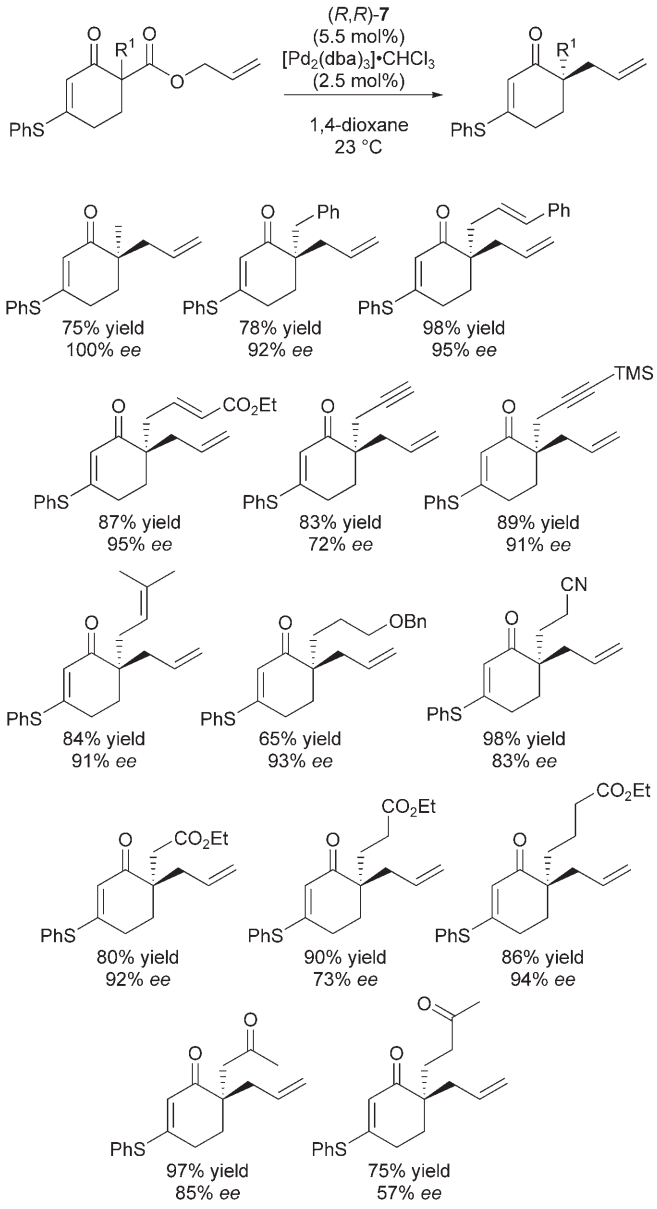
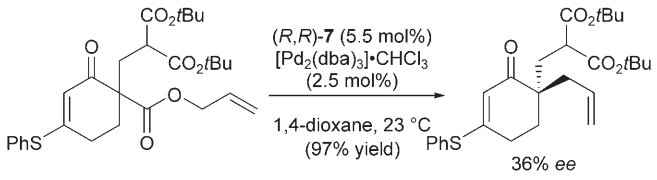


Scheme 16. Vinylogous thioesters prepared from allyl β-ketoesters.

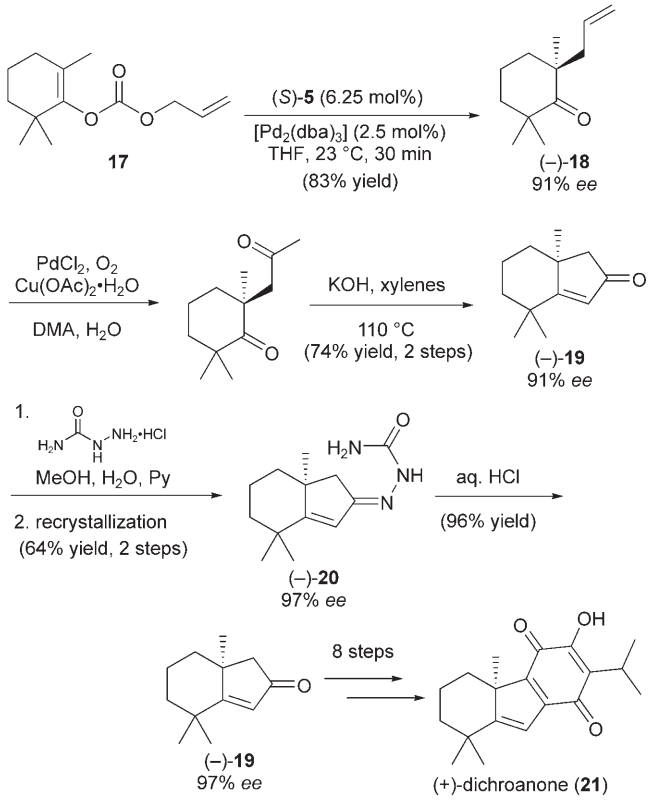


Scheme 17. Allylation in the presence of a pendant 1,3-diester.

5. Synthetic Applications of Enantioenriched Cycloalkanones

5.1. Total Synthesis of (+)-Dichroanone

Although the Tsuji allylation has seen only sparse use in total synthesis to date,[29] the prevalence of quaternary carbon stereocenters in natural products provides an ample proving ground for the utility of the enantioselective Tsuji allylation protocols described above. One class of compounds that bears this structural motif is a group of structurally similar norditerpenoids, which include the tricyclic *p*-quinone dichroanone (**21**; Scheme 18).[30] Recently, the enantioselective Tsuji allylation played a key role in the enantioselective total synthesis of (+)-dichroanone (**21**) by our group.[31]



Scheme 18. Enantioselective Tsuji allylation in the total synthesis of (+)-dichroanone. DMA = *N*,*N*-dimethylacetamide.

The synthesis commenced from allyl enol carbonate **17**, which underwent enantioselective Tsuji allylation to form ketone (−)-**18** with 91% *ee*. Attempts to form the corresponding semicarbazone derivative to improve the *ee* of this material (Scheme 5) were negated by the presence of two quaternary centers adjacent to the ketone. However, Wacker oxidation and aldol condensation led to bicyclic enone (−)-**19**, which readily formed semicarbazone derivative (−)-**20**. Recrystallization of this material and hydrolysis of the semicarbazone provided enone (−)-**19** with 97% *ee*. Conversion of bicycle (−)-**19** into **21** was achieved in eight steps. The material produced by this route was enantiomeric to the natural isolate, which was of unknown absolute configuration. Therefore, this total synthesis unambiguously proved the configuration of *nat*-(−)-(*S*)-dichroanone (**21**). Dichroanone was produced in 11 steps from commercially

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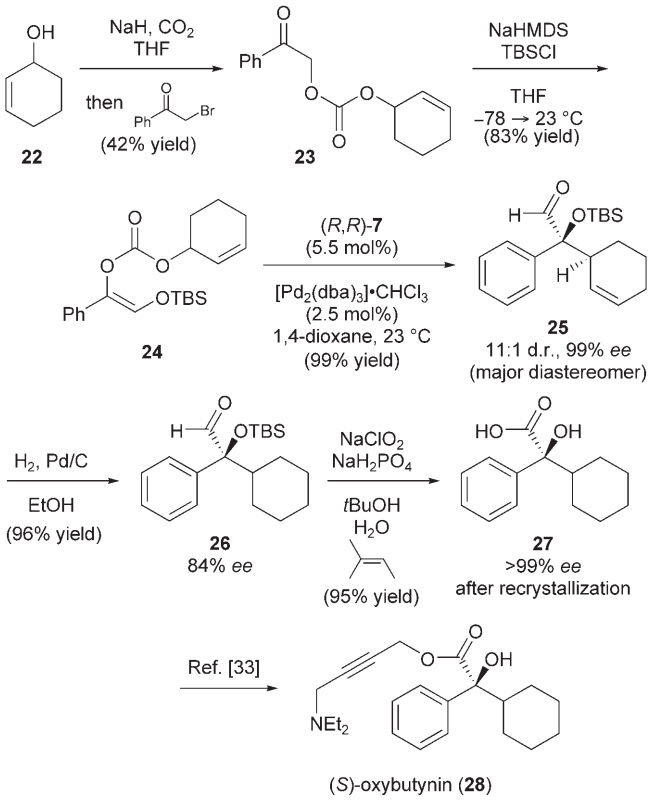
available material in 4% overall yield without the use of protecting groups.

5.2. Formal Synthesis of Oxybutynin

The reported conversion by Trost's group of allyl enol carbonates into α-hydroxy aldehydes[23] was highlighted by the formal synthesis of (*S*)-oxybutynin (**28**; Scheme 19), a pharmaceutical compound used to treat various urinary disorders. Although commercial oxybutynin is sold as a racemic mixture, some studies suggest that enantiopure (*S*)-oxybutynin may offer improved pharmaceutical properties. As a result, asymmetric methods of producing (*S*)-oxybutynin may become valuable.[32]



Scheme 19. Enantioselective formal synthesis of (*S*)-oxybutynin. HMDS = hexamethyldisilazane.

The synthesis began with the one-step formation of mixed carbonate **23** from alcohol **22**, CO_2, and α-bromoacetophenone. Treatment with base and TBSCl initiated a shift of the carbonate group, and the resulting aldehyde enolate was trapped as the enol silane **24**. Decarboxylative allylation was effected with Pd^0 supported by bisphosphine ligand (*R*,*R*)-**7** to yield α-tertiary aldehyde **25** as an 11:1 mixture of diastereomers. Although the *ee* of the major diastereomer was 99%, subsequent olefin hydrogenation of the diastereomeric mixture led to aldehyde **26** with 84% *ee*. Oxidation with concomitant silyl ether cleavage formed (*S*)-**27**, a known intermediate in the synthesis of oxybutynin;[33] recrystallization of (*S*)-**27** increased its *ee* from 84 to over 99%.

5.3. Progress Toward Zoanthenol

The zoanthus alkaloids are a family of polycyclic marine natural products with complex molecular architectures and interesting biological properties. These compounds have attracted significant attention from the synthetic community on the basis of their challenging structural features and their significant biological activity (antiosteoporotic, cytotoxic, antibacterial).[34] Despite the large body of work toward these natural products, only one member of the class, norzoanthamine, has had its total synthesis achieved.[35]

One of the greatest challenges posed by the zoanthus alkaloids is the three quaternary carbon stereocenters about the C ring. Our group recently reported an approach to the synthesis of one member of this class, zoanthenol (**38**; Scheme 20), and addressed these difficult stereocenters by an acid-mediated cyclization reaction to form the B ring.[36] The stereochemistry of the two stereocenters generated in this ring-forming reaction would ultimately be directed by the configuration of the quaternary stereocenter at C22.

To fully exploit the key diastereoselective steps of this synthetic approach, an enantioselective method to form the C22 quaternary carbon center was required. To this end, readily available allyl β-ketoester **29** was treated with catalytic $[Pd_2(dba)_3]$ and (*S*)-*t*BuPHOX to form ketone (−)-**30** in 94% yield and with 86% *ee*. Oxidative olefin cleavage followed by esterification and methylation formed ketone (+)-**31**, an immediate precursor to enol triflate **32**.

Toward the completion of the tricyclic core, racemic enol triflate **32** was converted into enal **33** through an interesting Pd-catalyzed reductive carbonylation. Highly diastereoselective addition of Grignard reagent **34** yielded cyclization precursor **35**, which, upon exposure to TFA, formed both the B ring and the key C12 quaternary stereocenter with good diastereocontrol. Further elaboration of tricycle **36** over nine steps led to diketone **37**, which bears the correct stereochemical triad for the natural product (confirmed by X-ray crystallography).

5.4 α-Fluorinated Cycloalkanones

Stereodefined α-fluoroketones are intriguing compounds for synthetic and medicinal chemistry. The asymmetric synthesis of such compounds, however, has been quite challenging.[37] The mild reaction conditions and functional-group tolerance of the Tsuji allylation protocol are ideal for the incorporation of fluorine atoms. Moreover, the facile fluorination of β-ketoesters with electrophilic reagents, such as Selectfluor, allows the straightforward preparation of fluorine-containing substrates.[38]

We reported the first use of the enantioselective Tsuji allylation to generate an enantioenriched tertiary fluoride with the preparation of 2-allyl-2-fluorocyclohexanone with 91% *ee* (Scheme 21).[26] Soon after, Nakamura and co-work-

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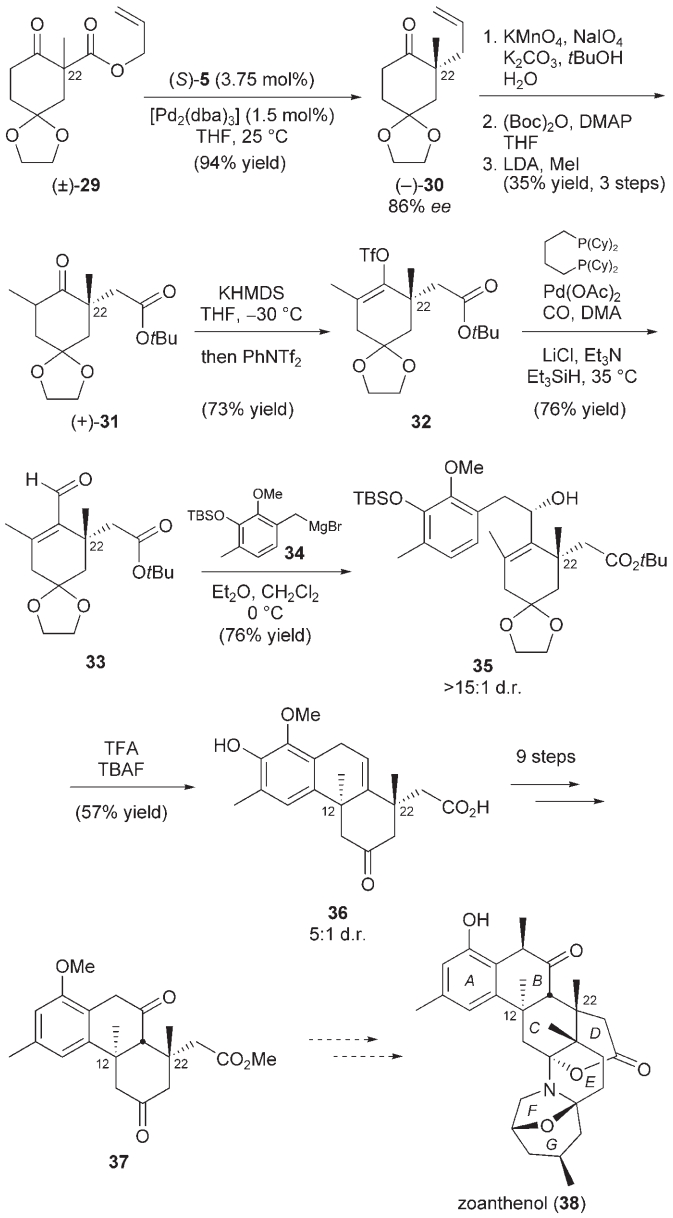
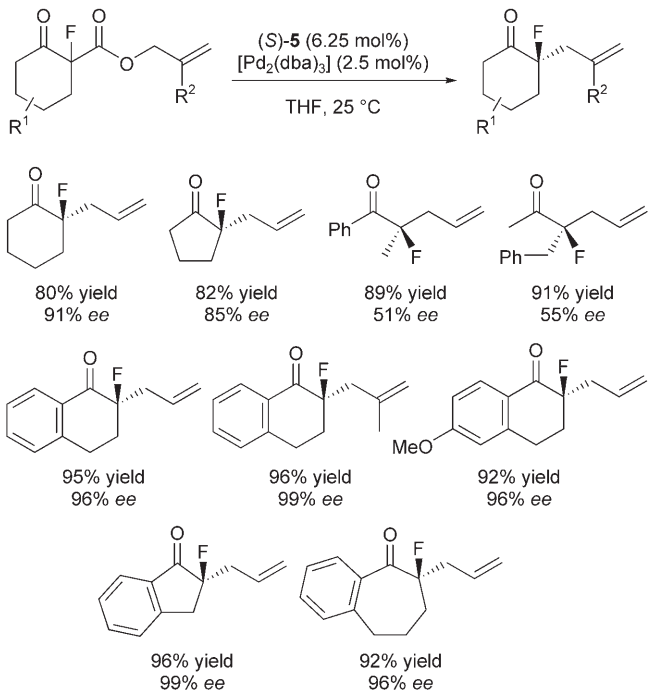


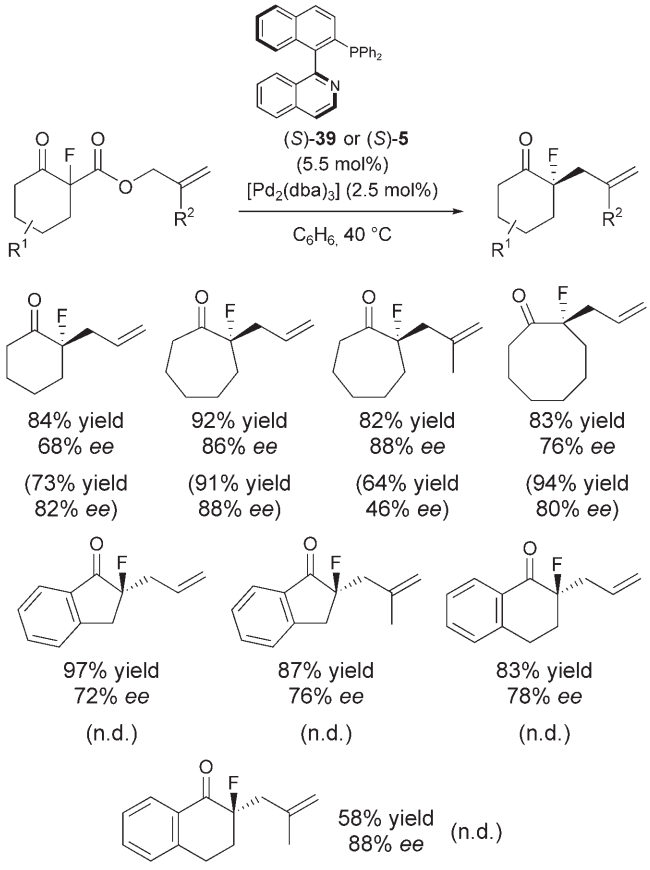
Scheme 20. Progress toward the total synthesis of zoanthenol. Boc = *tert*-butyloxycarbonyl, Cy = cyclohexyl, DMAP = 4-(dimethylamino)pyridine, LDA = lithium diisopropylamide, TBAF = tetrabutylammonium fluoride, Tf = trifluoromethanesulfonyl, TFA = trifluoroacetic acid.

ers elaborated this concept with a nearly identical catalyst system.[27] They found high levels of enantioselectivity for a range of cyclic substrates and modest enantioselectivity for acyclic β-ketoester substrates.

Since the appearance of the nearly simultaneous reports above, two other related systems have emerged. Tunge and co-workers also chose allyl β-ketoester substrates and found that the biaryl P/N chelating ligand QUINAP (**39**) provided good levels of enantioselectivity, although *t*BuPHOX (**5**) was superior in most cases (Scheme 22).[39] Notably, (*S*)-QUINAP ((*S*)-**39**) and (*S*)-*t*BuPHOX ((*S*)-**5**) provided products in the opposite enantiomeric series, an effect also observed by our group for allylation from allyl enol carbo-



Scheme 21. Enantioenriched α-fluoroketones derived from allyl β-ketoesters.



Scheme 22. Enantioenriched α-fluorocycloalkanones prepared from allyl β-ketoesters. Yields and *ee* values given are for (*S*)-**39** ((*S*)-**5** in parentheses).

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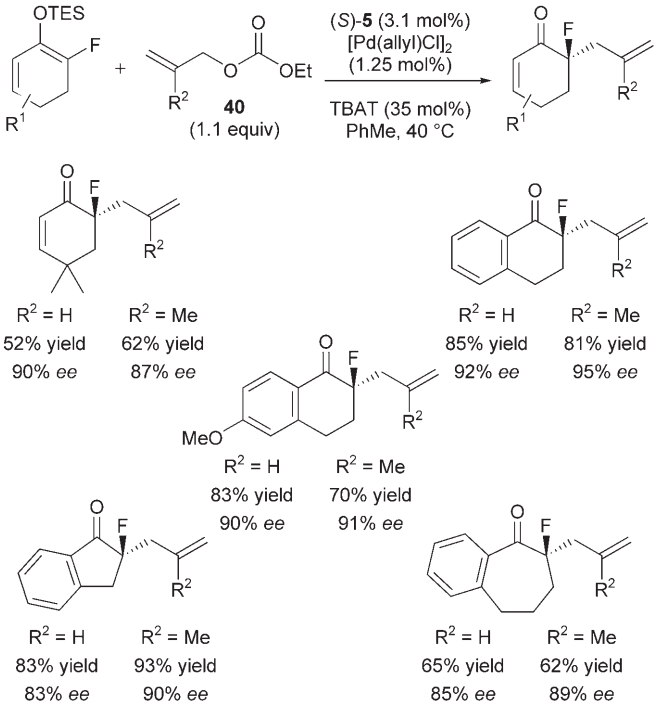
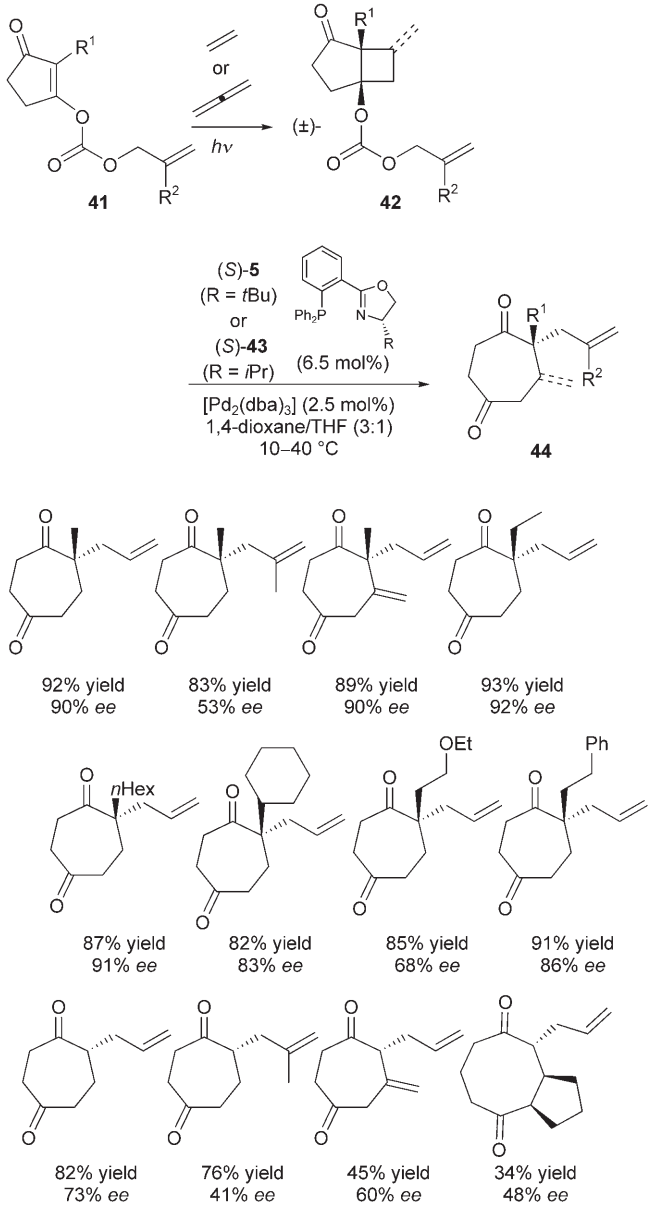
nates.[19] This shift in absolute configuration may be advantageous as (*R*)-*t*BuPHOX, which is derived from (*R*)-*tert*-leucine, is more expensive than its antipode, whereas both enantiomers of QUINAP are commercially available. In agreement with our findings and those of Nakamura and co-workers, P/P and P/O chelating ligands were found to be inferior to P/N ligands in terms of *ee*.

In 2007, Paquin and co-workers reported a system based on the silyl enol ether substrates employed by our group (see Section 3). The reaction conditions used in Paquin's work were slightly modified: $[Pd(allyl)Cl]_2$, toluene solvent, TES enol ethers in preference to TMS enol ethers, and allyl ethyl carbonates (**40**) in place of diallyl carbonates were used (Scheme 23).[40] Paquin and co-workers also found that (*S*)-**5** gave α-fluorocycloalkanones with high *ee*, whereas chelating P/P ligands performed poorly. However, their work has no examples of ketone enolates with multiple acidic sites.



Scheme 23. Enantioenriched α-fluorocycloalkanones prepared from silyl enol ethers. TES = triethylsilyl.



Scheme 24. Asymmetric ring-expanding allylation.

5.5. Cascade Reactions to Generate Enolates

An ingenious application of the allyl enol carbonate version of the Tsuji allylation was recently reported by Blechert's group (Scheme 24).[41] In this work, [3.2.0]bicycles **42** were readily synthesized through photocycloaddition from the corresponding allyl enol carbonates **41**. Subsequently, a retroaldol fragmentation cascade was initiated by decarboxylation of the allyl carbonate, and the resultant enolate underwent enantioselective allylation. As the substrate stereocenters are destroyed in the retroaldol step, racemic starting materials may be used, and the reaction is enantioconvergent. By exploiting this ring-expansion method, a variety of seven-membered-ring diketones **44** were generated with good *ee* by using the *t*BuPHOX/Pd^0 catalyst system. Attempts to generate tertiary stereocenters through this reaction were met with moderate *ee*, and in some cases it was necessary to employ (*S*)-*i*PrPHOX ((*S*)-**43**) to obtain reasonable yields. The overall sequence represents an enantioselective variant of the de Mayo reaction.[42]

This method allows access to interesting seven-membered-ring compounds that may be useful for the synthesis of a variety of natural products. Important to the develop-

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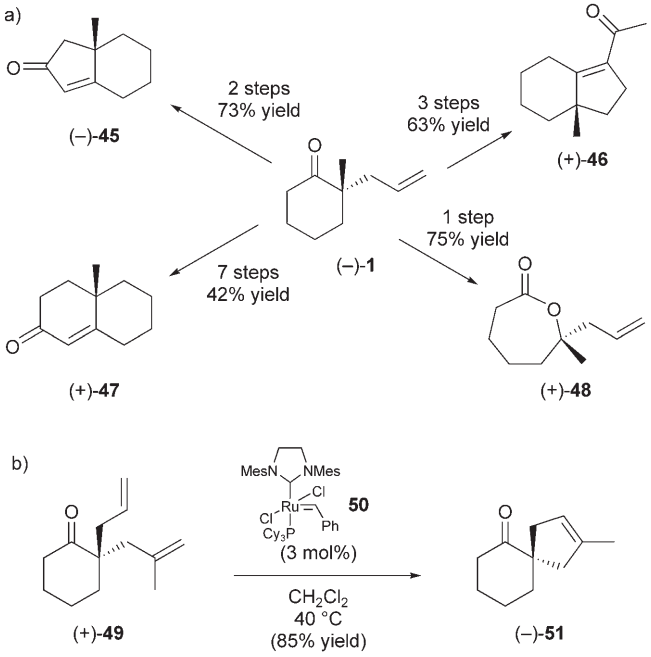
ment of the enantioselective allylation methodology, this work suggests that many distinct methods of accessing a Pd–enolate intermediate may be amenable to enantioselective reactions by using the ligand complexes discussed herein.

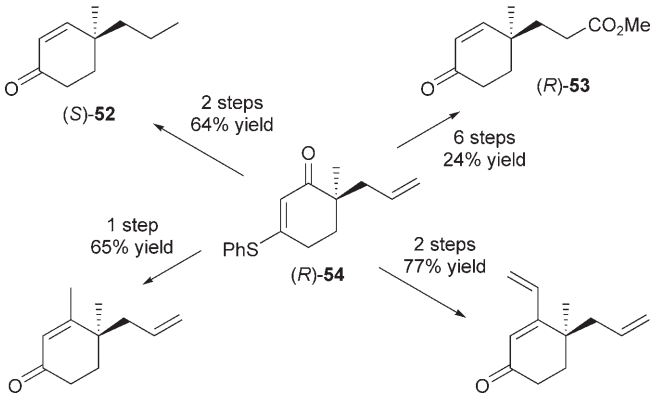
5.6. Miscellaneous Applications

In the initial report by our group, several useful transformations of the α-quaternary cycloalkanone products were carried out (Scheme 25a).[19] Among these were functionalizations of the allyl group followed by aldol condensation to generate [6.5] and [6.6] bicycles **45**, **46**, and **47** in good yields. Enone **47** is commonly produced by Robinson annulation[43] and has found many applications in synthesis.[44] Another simple transformation of 2-allyl-2-methylcyclohexanone (**1**) is the conversion into lactone **48** by Baeyer–Villiger oxidation. This transformation provides an entry to enantioenriched tertiary alcohol stereocenters. Spriocyclic systems were accessed with high *ee* by employing the Grubbs second-generation olefin-metathesis catalyst **50**[45] to transform ketone **49** into **51** (Scheme 25b).[24]



Scheme 25. a) Transformations of ketone (−)-**1**. b) Ring-closing metathesis to generate a spirocycle. Mes = mesityl.

The vinylogous thioesters produced by Trost et al. (Scheme 15) were amenable to further functionalization by Stork–Danheiser-type manipulations (Scheme 26).[46] These transformations provided a valuable route to enantioenriched γ-quaternary stereocenters in enone systems.[47] Two of these derivatives, (*S*)-**52** and (*R*)-**53**, were used to establish the absolute configuration of (*R*)-**54**.



Scheme 26. Stork–Danheiser-type transformations of vinylogous thioester (*R*)-**51**.

6. Mechanism of Allylation Reactions

To date, there has been relatively little mechanistic evidence presented for these reactions. One important set of experiments that have been reported are cross-over experiments. Both Trost's group and ours described cross-over experiments with enol carbonate substrates and their respective catalyst systems (Scheme 27). Trost's group observed minimal cross-over between allyl and crotyl carbonates (**55** and **57**, respectively);[21] they attributed the lack of cross-over with the bisphosphine/Pd^0 catalyst system to a rate of alkylation that exceeds the rate of ion diffusion from solvent-caged ion pairs in dioxane. Further evidence for the importance of these contact ion pairs was the importance of the solvent in suppressing overalkylation and enolate scrambling when forming tertiary stereocenters.[21,23]

In contrast to the results of Trost's group, we observed scrambling of allyl termini and complete cross-over between the two differently deuterated allyl enol carbonates **59** and **60** in THF, dioxane, and benzene (Scheme 27b).[26] Saegusa and co-workers also observed cross-over in a similar experiment with a non-enantioselective system and allyl β-ketoester substrates in DMF, although cross-over was suppressed in benzene.[14b] At the time, Saegusa and co-workers proposed a catalytic cycle similar to the one shown in Scheme 28 that accounted for cross-over at two stages in the process. This cycle appears to be consistent with the results obtained by us with the PHOX/Pd^0 catalyst system. Although our cross-over results clearly contrast with those of Trost's group, these experiments are not informative as to the mechanism of bond formation or the origin of enantioselectivity in these reactions.

The reversal of enantioselectivity that Trost et al. observed between the reaction of pregenerated lithium enolates[6a] and those generated in situ from allyl enol carbonates[21] indicates that these two processes probably have significantly different mechanisms. However, the details of these differences have not been elucidated experimentally. The possible intermediacy of an inner-sphere Pd enolate[48] rather than the outer-sphere nucleophile typical of other π-

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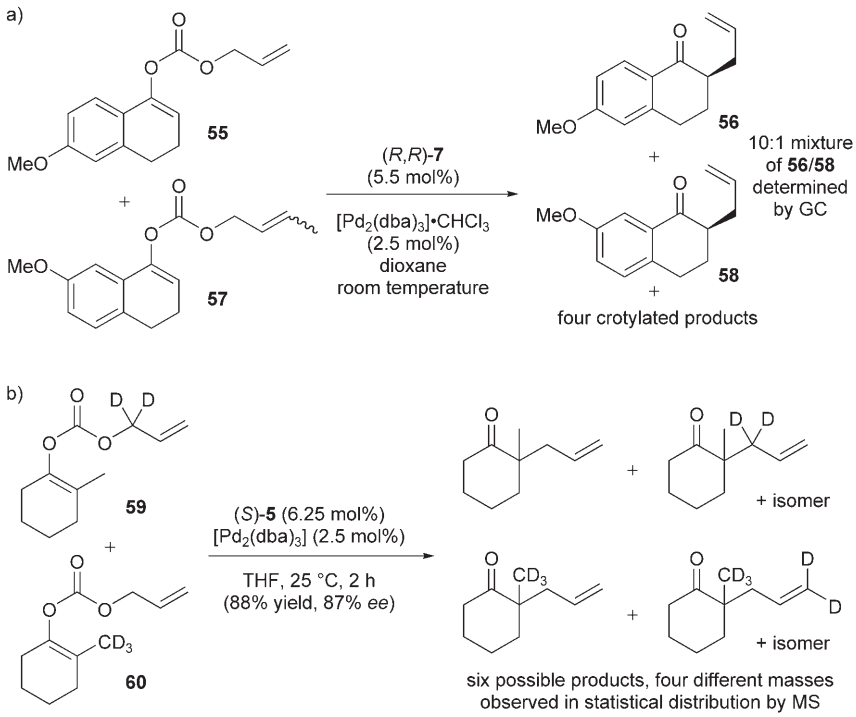
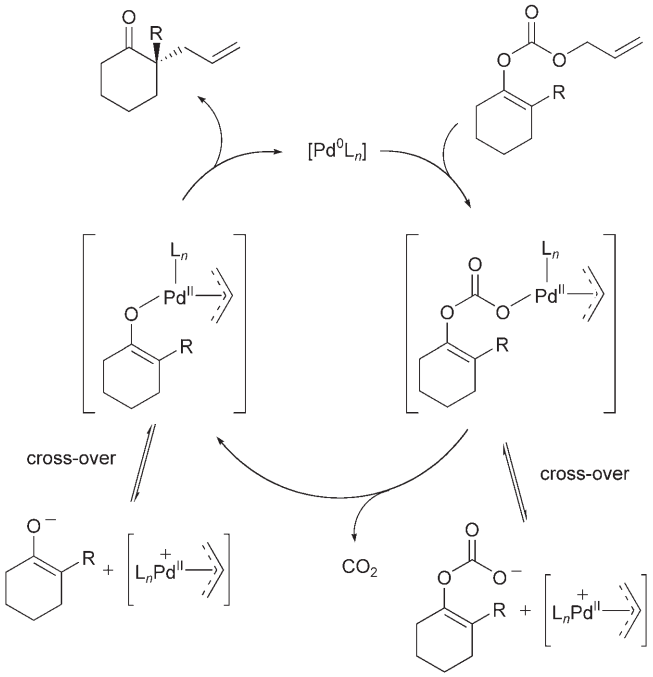


Scheme 27. a) The Trost cross-over experiment. b) Our cross-over experiment.

allyl alkylations[49] has been suggested, though not proven. The lack of enolate scrambling observed throughout all the studies presented herein, especially in the presence of an acidic 1,3-diester moiety (Scheme 17), would be consistent with the inner-sphere proposal.



Scheme 28. Possible catalytic cycle for decarboxylative allylation.

Conclusions

The important discoveries made by Prof. Tsuji and his coworkers laid the groundwork for a multitude of useful processes that will surely find further applications in the coming years. These powerful methods allow for the high-yield synthesis of α-quaternary cycloalkanones from three distinct substrate motifs. Apart from quaternary centers, several examples of the synthesis of tertiary stereocenters have been reported. The versatility of these methods provides valuable inroads toward the ultimate goal of general protocols for the enantioselective functionalization of enolates. The first evidence of the impact of these methods is apparent in the applications to total synthesis and to the synthesis of other important functionalized molecules described in this Focus Review. The adaptations of other palladium enolate reactions developed by Tsuji to analogous enantioselective variants (e.g., enantioselective protonation[50]) are indicative of the ongoing legacy of these contributions. We anticipate a multitude of future reports on the utility of these reactions that will further demonstrate the importance of the pioneering discoveries of Prof. Tsuji.

Acknowledgements

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[1] For excellent general reviews on the catalytic enantioselective generation of quaternary stereocenters, see: a) B. M. Trost, C. Jiang, *Synthesis* **2006**, 369–396; b) *Quaternary Stereocenters: Challenges and Solutions for Organic Synthesis* (Eds: J. Christoffers, A. Baro), Wiley, Weinheim, **2005**; c) C. J. Douglas, L. E. Overman, *Proc. Natl. Acad. Sci. USA* **2004**, *101*, 5363–5367; d) I. Denissova, L. Barriault, *Tetrahedron* **2003**, *59*, 10105–10146; e) J. Christoffers, A. Mann, *Angew. Chem.* **2001**, *113*, 4725–4732; *Angew. Chem. Int. Ed.* **2001**, *40*, 4591–4597; f) E. J. Corey, A. Guzman-Perez, *Angew. Chem.* **1998**, *110*, 402–415; *Angew. Chem. Int. Ed.* **1998**, *37*, 388–401; g) K. Fuji, *Chem. Rev.* **1993**, *93*, 2037–2066; h) S. F. Martin, *Tetrahedron* **1980**, *36*, 419–460.
[2] T. Hayashi, K. Kanehira, T. Hagihara, M. Kumada, *J. Org. Chem.* **1988**, *53*, 113–120.
[3] a) M. Sawamura, H. Nagata, H. Sakamoto, Y. Ito, *J. Am. Chem. Soc.* **1992**, *114*, 2586–2592; b) M. Sawamura, M. Sudoh, Y. Ito, *J. Am. Chem. Soc.* **1996**, *118*, 3309–3310; c) R. Kuwano, Y. Ito, *J. Am.*

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Chem. Soc. **1999**, *121*, 3236–3237; d) R. Kuwano, K. Uchida, Y. Ito, *Org. Lett.* **2003**, *5*, 2177–2179.
[4] a) B. M. Trost, G. M. Schroeder, J. Kristensen, *Angew. Chem.* **2002**, *114*, 3642–3645; *Angew. Chem. Int. Ed.* **2002**, *41*, 3492–3495; b) B. M. Trost, R. Radinov, E. M. Grenzer, *J. Am. Chem. Soc.* **1997**, *119*, 7879–7880; c) B. M. Trost, X. Ariza, *Angew. Chem.* **1997**, *109*, 2749–2751; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2635–2637.
[5] S.-L. You, X.-L. Hou, L.-X. Dai, B.-X. Cao, J. Sun, *Chem. Commun.* **2000**, 1933–1934.
[6] a) B. M. Trost, G. M. Schroeder, *J. Am. Chem. Soc.* **1999**, *121*, 6759–6760; b) B. M. Trost, G. M. Schroeder, *Chem. Eur. J.* **2005**, *11*, 174–184.
[7] S.-L. You, X.-L. Hou, L.-X. Dai, X.-Z. Zhu, *Org. Lett.* **2001**, *3*, 149–151.
[8] Significant progress has also been made for the Pd-catalyzed alkylation of pregenerated, unstabilized enolates to generate tertiary stereocenters. However, these are beyond the scope of this Focus Review as they are not based on Tsuji's work; see: a) M. Braun, F. Laicher, T. Meier, *Angew. Chem.* **2000**, *112*, 3637–3640; *Angew. Chem. Int. Ed.* **2000**, *39*, 3494–3497; b) X.-X. Yan, C.-G. Liang, Y. Zhang, W. Hong, B.-X. Cao, L.-X. Dai, X.-L. Hou, *Angew. Chem.* **2005**, *117*, 6702–6704; *Angew. Chem. Int. Ed.* **2005**, *44*, 6544–6546.
[9] For an outstanding review of this topic, see: U. Kazmaier, *Curr. Org. Chem.* **2003**, *7*, 317–328.
[10] Apart from the work discussed in this Focus Review, two other notable enantioselective catalyst systems capable of generating α-quaternary cycloalkanones have been reported. For a method for alkylation of lithium enolates with a catalytic oligoamine ligand, see: a) Y. Yamashita, K. Odashima, K. Koga, *Tetrahedron Lett.* **1999**, *40*, 2803–2806; for a method that employs pregenerated tin enolates, a variety of electrophiles, and a chromium catalyst, see: b) A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2005**, *127*, 62–63; for application of a Cr catalyst to acyclic alkylation of tin enolates, see: c) A. G. Doyle, E. N. Jacobsen, *Angew. Chem.* **2007**, *119*, 3775–3779; *Angew. Chem. Int. Ed.* **2007**, *46*, 3701–3705.
[11] For a profile of the career of Prof. Jiro Tsuji, see: Y. Yamamoto, *J. Organomet. Chem.* **1999**, *576*, xi-xiii.
[12] J. Tsuji, I. Minami, I. Shimizu, *Tetrahedron Lett.* **1983**, *24*, 1793–1796.
[13] J. Tsuji, I. Minami, I. Shimizu, *Chem. Lett.* **1983**, 1325–1326.
[14] a) I. Shimizu, T. Yamada, J. Tsuji, *Tetrahedron Lett.* **1980**, *21*, 3199–3202; Saegusa and co-workers published very similar work with β-ketoesters simultaneously; see: b) T. Tsuda, Y. Chujo, S.-i. Nishi, K. Tawara, T. Saegusa, *J. Am. Chem. Soc.* **1980**, *102*, 6381–6384.
[15] J. Tsuji, I. Minami, I. Shimizu, *Tetrahedron Lett.* **1983**, *24*, 4713–4714.
[16] For an excellent general review of metal-catalyzed decarboxylative enolate functionalization, see: J. A. Tunge, E. C. Burger, *Eur. J. Org. Chem.* **2005**, 1715–1726.
[17] a) J. Tsuji, *Acc. Chem. Res.* **1969**, *2*, 144–152; b) J. Tsuji, *Pure Appl. Chem.* **1982**, *54*, 197–206; c) J. Tsuji, *Pure Appl. Chem.* **1986**, *58*, 869–878; d) J. Tsuji, I. Minami, *Acc. Chem. Res.* **1987**, *20*, 140–145; e) J. Tsuji, *Pure Appl. Chem.* **1989**, *61*, 1673–1680; f) J. Tsuji, *Pure Appl. Chem.* **1999**, *71*, 1539–1547; g) J. Tsuji, *New J. Chem.* **2000**, *24*, 127–135; h) J. Tsuji, *Proc. Jpn. Acad. Ser. B* **2004**, *80*, 349–358.
[18] For other reviews on closely related topics, see: a) M. Braun, T. Meier, *Synlett* **2006**, 661–676; b) S.-L. You, L.-X. Dai, *Angew. Chem.* **2006**, *118*, 5372–5374; *Angew. Chem. Int. Ed.* **2006**, *45*, 5246–5248; c) M. Braun, T. Meier, *Angew. Chem.* **2006**, *118*, 7106–7109; *Angew. Chem. Int. Ed.* **2006**, *45*, 6952–6955.
[19] D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2004**, *126*, 15044–15045.
[20] a) G. Helmchen, A. Pfaltz, *Acc. Chem. Res.* **2000**, *33*, 336–345; b) J. M. J. Williams, *Synlett* **1996**, 705–710, and references therein.
[21] B. M. Trost, J. Xu, *J. Am. Chem. Soc.* **2005**, *127*, 2846–2847.
[22] B. M. Trost, J. Xu, M. Reichle, *J. Am. Chem. Soc.* **2007**, *129*, 282–283.
[23] B. M. Trost, J. Xu, *J. Am. Chem. Soc.* **2005**, *127*, 17180–17181.
[24] D. C. Behenna, PhD thesis, California Institute of Technology (USA), **2006**.
[25] For a discussion of double stereodifferentiation, see: E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, pp. 965–971.
[26] J. T. Mohr, D. C. Behenna, A. M. Harned, B. M. Stoltz, *Angew. Chem.* **2005**, *117*, 7084–7087; *Angew. Chem. Int. Ed.* **2005**, *44*, 6924–6927.
[27] M. Nakamura, A. Hajra, K. Endo, E. Nakamura, *Angew. Chem.* **2005**, *117*, 7414–7417; *Angew. Chem. Int. Ed.* **2005**, *44*, 7248–7251.
[28] B. M. Trost, R. N. Bream, J. Xu, *Angew. Chem.* **2006**, *118*, 3181–3184; *Angew. Chem. Int. Ed.* **2006**, *45*, 3109–3112.
[29] For examples of Tsuji enol carbonate allylations in synthesis, see: a) P. M. Herrinton, K. L. Klotz, W. M. Hartley, *J. Org. Chem.* **1993**, *58*, 678–682; b) K. C. Nicolaou, G. Vassilikogiannakis, W. Mägerlein, R. Kranich, *Angew. Chem.* **2001**, *113*, 2543–2547; *Angew. Chem. Int. Ed.* **2001**, *40*, 2482–2486; c) N. Ohmori, *J. Chem. Soc. Perkin Trans. 1* **2002**, 755–767.
[30] For isolation of dichroanone and related natural products, see: a) K. Kawazoe, M. Yamamoto, Y. Takaishi, G. Honda, T. Fujita, E. Sezik, E. Yesilada, *Phytochemistry* **1999**, *50*, 493–497; b) W.-H. Lin, J.-M. Fang, Y.-S. Cheng, *Phytochemistry* **1995**, *40*, 871–873; c) W.-H. Lin, J.-M. Fang, Y.-S. Cheng, *Phytochemistry* **1996**, *42*, 1657–1663; d) H. Ohtsu, M. Iwamoto, H. Ohishi, S. Matsunaga, R. Tanaka, *Tetrahedron Lett.* **1999**, *40*, 6419–6422; e) C.-I. Chang, S.-C. Chien, S.-M. Lee, Y.-H. Kuo, *Chem. Pharm. Bull.* **2003**, *51*, 1420–1422; f) C.-I. Chang, J.-Y. Chang, C.-C. Kuo, W.-Y. Pan, W.-Y. Kuo, *Planta Med.* **2005**, *71*, 72–76.
[31] R. M. McFadden, B. M. Stoltz, *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739.
[32] For other recent synthetic routes to oxybutynin, see: a) C. H. Senanayake, Q. K. Fang, P. Grover, R. P. Bakale, C. P. Vandenbossche, S. A. Wald, *Tetrahedron Lett.* **1999**, *40*, 819–822; b) P. T. Grover, N. H. Bhongle, S. A. Wald, C. H. Senanayake, *J. Org. Chem.* **2000**, *65*, 6283–6287; c) S. Masumoto, M. Suzuki, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2002**, *43*, 8647–8651; d) P. Gupta, R. A. Fernandes, P. Kumar, *Tetrahedron Lett.* **2003**, *44*, 4231–4232; e) S. Masumoto, M. Suzuki, M. Kanai, M. Shibasaki, *Tetrahedron* **2004**, *60*, 10497–10504; f) O. Tokuda, T. Kano, W.-G. Gao, T. Ikemoto, K. Maruoka, *Org. Lett.* **2005**, *7*, 5103–5105.
[33] R. P. Bakale, J. L. Lopez, F. X. McConville, C. P. Vandenbossche, C. H. Senanayake (Sepracor, Inc.), US Patent 6140529, **2000**.
[34] For a comprehensive examination of the zoanthus alkaloids and synthetic approaches, see: D. C. Behenna, J. L. Stockdill, B. M. Stoltz, *Angew. Chem. Int. Ed.*, DOI: 10.1002/anie.200703172.
[35] M. Miyashita, M. Sasaki, I. Hattori, M. Sakai, K. Tanino, *Science* **2004**, *305*, 495–499.
[36] D. C. Behenna, J. L. Stockdill, B. M. Stoltz, *Angew. Chem.* **2007**, *119*, 4155–4158; *Angew. Chem. Int. Ed.* **2007**, *46*, 4077–4080.
[37] For a recent review of asymmetric approaches to these compounds, see: G. K. S. Prakash, P. Beier, *Angew. Chem.* **2006**, *118*, 2228–2230; *Angew. Chem. Int. Ed.* **2006**, *45*, 2172–2174, and references therein.
[38] For representative examples of electrophilic fluorinating agents, see: a) T. Umemoto, S. Fukami, G. Tomizawa, K. Harasawa, K. Kawada, K. Tomita, *J. Am. Chem. Soc.* **1990**, *112*, 8563–8575; b) R. E. Banks, N. J. Lawrence, A. L. Popplewell, *J. Chem. Soc. Chem. Commun.* **1994**, 343–344; c) S. Stavber, M. Zupan, *Tetrahedron Lett.* **1996**, *37*, 3591–3594.
[39] E. C. Burger, B. R. Barron, J. A. Tunge, *Synlett* **2006**, 2824–2826.
[40] É. Bélanger, K. Cantin, O. Messe, M. Tremblay, J.-F. Paquin, *J. Am. Chem. Soc.* **2007**, *129*, 1034–1035.
[41] S. R. Schulz, S. Blechert, *Angew. Chem.* **2007**, *119*, 4040–4044; *Angew. Chem. Int. Ed.* **2007**, *46*, 3966–3970.
[42] M. T. Crimmins, *Chem. Rev.* **1988**, *88*, 1453–1473, and references therein.
[43] Several protocols for this reaction have been developed; for representative examples, see: a) E. C. Du Feu, F. J. McQuillin, R. Robinson, *J. Chem. Soc.* **1937**, 53–60; b) B. Gaspert, T. G. Halsall, D. Willis, *J. Chem. Soc.* **1958**, 624–628; c) J. A. Marshall, W. I. Fanta, *J.*

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Org. Chem. **1964**, *29*, 2501–2505; d) C. H. Heathcock, J. E. Ellis, J. E. McMurry, A. Coppolino, *Tetrahedron Lett.* **1971**, *12*, 4995–4996; e) G. Revial, M. Pfau, *Organic Syntheses*, *Vol. 9*, John Wiley & Sons, New York, **1998**, pp. 610–618.

[44] For some transformations of this key intermediate, see: D. L. Boger, *Modern Organic Synthesis: Lecture Notes*, TSRI Press, La Jolla, **1999**, pp. 273–281.

[45] M. Scholl, S. Ding, C. W. Lee, R. H. Grubbs, *Org. Lett.* **1999**, *1*, 953–956.

[46] G. Stork, R. L. Danheiser, *J. Org. Chem.* **1973**, *38*, 1775–1776.

[47] Fuchs and co-workers reported an effective catalytic enantioselective synthesis of γ-substituted enones, but this method is limited to tertiary stereocenters; see: J. Evarts, E. Torres, P. L. Fuchs, *J. Am. Chem. Soc.* **2002**, *124*, 11093–11101, and references therein.

[48] Following the submission of this Focus Review, an initial report of a computational model for the mechanism of the enantioselective Tsuji allylation with PHOX ligands has appeared. These calculations suggest that the inner-sphere mechanism is lower in energy than the competing outer-sphere pathway; see: J. A. Keith, D. C. Behenna, J. T. Mohr, S. Ma, S. C. Marinescu, J. Oxgaard, B. M. Stoltz, W. A. Goddard III, *J. Am. Chem. Soc.* **2007**, *129*, 11876–11877.

[49] For a representative study whereby a PHOX/Pd^0 catalyst system was found to proceed by an outer-sphere mechanism, see: a) H. Steinhagen, M. Regglin, G. Helmchen, *Angew. Chem.* **1997**, *109*, 2199–2202; *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2108–2110; b) G. Helmchen, H. Steinhagen, M. Reggelin, S. Kudis in *Selective Reactions of Metal-Activated Molecules* (Eds: H. Werner, P. Schreier), Vieweg Verlag, Wiesbaden, **1998**, pp. 205–215.

[50] J. T. Mohr, T. Nishimata, D. C. Behenna, B. M. Stoltz, *J. Am. Chem. Soc.* **2006**, *128*, 11348–11349.

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