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Enantioselective Tsuji Allylations

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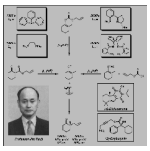
Abstract



The family of allylation reactions developed by Tsuji in the 1980's 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 has been 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; palladium; asymmetric catalysis; enols; ketones

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 carbons 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] Hou, and Dai[5] (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] Hou, and Dai[7] described palladium-catalyzed systems capable of generating quaternary stereocenters in high ee from unstabilized ketone enolates containing a single acidic position (e.g., tetralones, Scheme 1b).[8,9] Although

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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 in order to prevent the formation of mixtures of allylated products from in situ enolate scrambling.[1b] To highlight 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]

1.2 History

In the 1980's, Prof. Jiro Tsuji[11] and his coworkers 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 has published several accounts of his work in the development of this suite of reactions.[17]

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 to 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.

Over the past three years, a significant effort has been underway to develop enantioselective variants of the Tsuji reactions in order 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 of this review, 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 produced as a byproduct, the enolate 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, Stoltz reported an enantioselective Tsuji allylation from allyl enol carbonate substrates.[19] The initial screen 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*-Bu-PHOX, **5**) ligand framework, developed in the 1990's by Pfaltz, Helmchen, and Williams,[20] led to the formation of the elusive 2-allyl-2-methylcyclohexanone (**1**) in up to 89% ee, the first reported synthesis of this simple enantioenriched ketone.

The elaboration of this result to more complex systems proved rewarding. The mild reaction conditions were tolerant of a variety of substitution and functional groups (Scheme 4). Remarkably, these adapted enantioselective Tsuji allylation conditions were capable of generating a quaternary stereocenter adjacent to another quaternary carbon 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 proved to be nearly equally effective for several substrates, including ethereal (THF, 1,4-dioxane, Et_2O, *tert*-butyl methyl ether, *i*-Pr_2O), aromatic (benzene, toluene), and carbonyl containing (EtOAc) solvents.

In order to improve the enantiomeric excess of the cycloalkanone products, a straightforward method of derivitization to the corresponding semicarbazone followed by recrystallization and hydrolysis was developed. This protocol allows isolation of 2-allyl-2-methylcyclohexanone (**1**) in 98% ee (Scheme 5).

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 Stoltz, Trost identified that the uniquely shaped P/P ligand (*R*,*R*)-**7** provided high ee in the allylic alkylation of allyl enol carbonate substrates in toluene solvent (Scheme 6). Two examples of substrates with multiple sites of similar acidity were reported. Interestingly, in addition to the enantioselective formation of quaternary centers, the use of trisubstituted enol precursors led to the formation of highly enantioenriched tertiary stereocenters. Further optimization of reaction conditions was required in some cases in order to prevent multiple alkylations at the carbonyl α-position of these trisubstituted enol precursors; use of 1,4-dioxane solvent effectively suppressed over-alkylation for some substrates. Also included are the first examples of heterocycles in allylations of this type.[22]

An important facet of this chemistry was the observation that the major enantiomer of cycloalkanone product was of the opposite sense to that observed in the earlier work of Trost 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 the reaction with in situ generated Pd-enolate.

2.2 Synthesis of Acyclic Ketones and Aldehydes

A significant advance in the development of these protocols was the extension to acyclic enolate precursors. Trost found that many α-tertiary ketones could be formed with high ee 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 suggested 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 that identified siloxy substituted allyl enol carbonates were 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**, derived from a probable aldehyde enolate intermediate (**12**, Scheme 9). This most likely occured 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.

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

In addition to the allyl enol carbonate substrates, Stoltz has demonstrated the application of the PHOX/Pd^0 catalyst system to a variety of silyl enol ethers.[19,24] These enol silanes are desireable enolate precursors since 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 required the addition of a diallyl carbonate (**13**, Scheme 11) as a coupling partner. While Tsuji reported the allylation of silyl enol ethers without an exogenous activator,[13] it was found that the addition of a sub-stoichiometric amount of 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 using this catalyst system. This consistent enantioselectivity suggests that the mechanisms of C–C bond formation for both enolate precursors are identical.

While this substrate class 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. Additionally, this method has recently seen use in the synthesis of stereodefined tertiary fluorides (see Section 5.4).

4. Allyl β-Ketoesters

While 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 provided 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 led to mixtures of allylated products, and thus poor yield. An example is shown in Scheme 12.

When confronted with this problem, Stoltz found a possible solution in the work of Tsuji and Saegusa: allyl β-ketoesters, like the allyl enol carbonate substrates, contain all of 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] In the event, however, substrate kinetic resolution was not observed, and the desired products were formed in excellent yield and good ee (Scheme 13); this transformation of a racemic substrate to an enantioenriched product is an example of an enantioconvergent catalytic reaction.[26] The reaction likely proceeded through Pd-mediated oxidative addition and deallylation of the substrate followed by stereoablative C–C bond cleavage via decarboxylation, forming an achiral enolate intermediate, and finally 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 high ee. Interestingly, substrates bearing β-leaving groups did not suffer elimination, and substrates containing other acidic functional groups (e.g., nitrile, ester) did not cause enolate scrambling. Additionally, allyl

groups substituted at the central carbon (e.g., methyl, chloro) led to increased ee. The ketones produced from allyl β-ketoesters, allyl enol carbonates, and silyl enol ethers 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 Nakamura's work, three examples of quaternary stereocenter formation from allyl β-ketoesters were included as well.[27]

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

Subsequent to this initial report, Trost described application of the bisphosphine/Pd^0 catalyst to the enantioselective allylic alkylation of vinylogous ester and thioester enolates.[28] When Trost was confronted with a similar problem of non-selective 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 high ee products were obtained in many cases (Scheme 16). Details of the synthetic utility of these products are shown in Section 5.6.

Trost suggested that substrates bearing nearby Lewis basic groups (e.g., alkyne or carbonyl) 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 the Stoltz work, where neighboring Lewis basic groups had little effect (Cf. 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 is decreased considerably (Scheme 17).

Allyl β-ketoester substrates are very practical because of the simple substrate preparation, the benchtop 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 conversion of racemic materials to valuable enantioenriched products.

5. Synthetic Applications of Enantioenriched Cycloalkanones

5.1 Total Synthesis of (+)-Dichroanone

While 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 including 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 Stoltz.[31]

The synthesis commenced from allyl enol carbonate **17**, which underwent enantioselective Tsuji allylation to form ketone (–)-**18** in 91% ee. Attempts to form the corresponding semicarbazone derivative in order to improve the ee of this material (see 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 a semicarbazone derivative ((–)-**20**). Recrystallization of this material and hydrolysis of the semicarbazone provided enone (–)-**19** in 97% ee. Conversion of bicycle (–)-**19** to (+)-dichroanone (**21**) was achieved in 8 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 available material in 4% overall yield without the use of protecting groups.

5.2 Formal Synthesis of Oxybutynin

Trost's reported conversion of allyl enol carbonates to 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. While 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]

The synthesis began with 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**, yielding 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** in 84% ee. Oxidation with concomitant silyl ether cleavage formed (*S*)-**27**, a known intermediate in the synthesis of oxybutynin,[33] which could be recrystallized from 84% to >99% ee.

5.3 Progress Toward Zoanthenol

The zoanthus alkaloids are a family polycyclic marine natural products with complex molecular architecture and interesting biological properties. These compounds have attracted significant attention from the synthetic community based on the 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 succumbed to total synthesis.[35]

One of the greatest challenges posed by the zoanthus alkaloids is the three quaternary carbon stereocenters about the C ring. Stoltz recently reported an approach to the synthesis of one member of this class, zoanthenol (**38**, Scheme 20), and addressed these difficult stereocenters via 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 C(22).

In order to fully exploit the key diastereoselective steps of this synthetic approach, an enantioselective method to form the C(22) 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*-Bu-PHOX to form ketone (–)-**30** in 94% yield and 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 to enal **33** through an interesting Pd-catalyzed reductive carbonylation. Highly diastereoselective addition of Grignard reagent **34** yielded cyclization precursor **35**, which, upon exposure to trifluoroacetic acid (TFA), formed both the B ring and the key C(12) quaternary stereocenter with good diastereocontrol. Further elaboration of tricycle **36** over 9 steps led to diketone **37**, which bore 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 straightforward preparation of fluorine containing substrates.[38]

Stoltz reported the first use of the enantioselective Tsuji allylation to generate an enantioenriched tertiary fluoride with the preparation of 2-allyl-2-fluorocyclohexanone in 91% ee (Scheme 21).[26] Soon thereafter, Nakamura elaborated this concept with a nearly identical catalyst system.[27] In his work, Nakamura 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 appeared. Tunge also chose allyl β-ketoester substrates and found that the biaryl P/N chelating ligand QUINAP (**39**) provided good levels of enantioselectivity, although *t*-Bu-PHOX (**5**) was superior in most cases (Scheme 22).[39] Notably, (*S*)-QUINAP ((*S*)-**39**) and (*S*)-*t*-Bu-PHOX ((*S*)-**5**) provided products in the opposite enantiomeric series, an effect also observed by Stoltz for allylation from allyl enol carbonates.[19] This shift in absolute configuration may be advantageous since (*R*)-*t*-Bu-PHOX, derived from (*R*)-*t*-leucine, is more expensive than its antipode, while both enantiomers of QUINAP are commercially available. In agreement with the findings of Stoltz and Nakamura, P/P and P/O chelating ligands were found to be inferior to P/N ligands in terms of ee.

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

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 (Scheme 24).[41] In this work, [3.2.0]bicycles (**42**) were readily synthesized via photocycloaddition from the corresponding allyl enol carbonates (**41**). Subsequently, a retro-aldol fragmentation cascade was initiated by decarboxylation of the allyl carbonate and the resultant enolate underwent enantioselective allylation. Since the substrate stereocenters are destroyed in the retro-aldol step, racemic starting materials may be used and the reaction is enantioconvergent. Exploiting this ring-expansion method, a variety of 7-membered ring diketones (**44**) were generated in good ee using the *t*-Bu-PHOX/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*-Pr-PHOX ((*S*)-**43**) in order to

obtain reasonable yields. The overall sequence represents an enantioselective variant of the de Mayo reaction.[42]

This method allows access to interesting 7-membered ring compounds that may be useful for the synthesis of a variety of natural products. Important to the development of the enantioselective allylation methodology, this work suggests that many distinct methods of accessing a Pd-enolate intermediate may be amenable to enantioselective reactions using the ligand complexes discussed in this review.

5.6 Miscellaneous Applications

In the initial report by Stoltz, 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**) has commonly been produced by Robinson annulation[43] and has found many applications in synthesis.[44] Another simple transformation of 2-allyl-2-methylcyclohexanone (**1**) was the conversion to lactone **48** via Baeyer-Villiger oxidation. This transformation provides an entry to enantioenriched tertiary alcohol stereocenters. Spriocyclic systems were accessed in high ee by employing Grubbs' second generation olefin metathesis catalyst (**50**)[45] to transform ketone **49** into **51** (Scheme 25b).[24]

The vinylogous thioesters produced by Trost (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**.

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 crossover experiments. Both Trost and Stoltz described crossover experiments with enol carbonate substrates and their respective catalyst systems (Scheme 27). Trost observed minimal crossover between allyl and crotyl carbonates (**55** and **57**, respectively).[21] Trost attributed the lack of crossover 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 solvent in suppressing over-alkylation and enolate scrambling when forming tertiary stereocenters.[21,23]

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

The reversal of enantioselectivity Trost observed between the reaction of pre-generated lithium enolates[6a] and those generated in situ from allyl enol carbonates[21] indicates that these two processes likely have significantly different mechanisms. However, the details of these differences have not been elucidated experimentally. The possible intermediacy of an inner-

sphere Pd-enolate rather than the outer-sphere nucleophile typical of other π-allyl alkylations [48] has been suggested, though not proven. The lack of enolate scrambling observed throughout all of 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.

Conclusion

The important discoveries made by Prof. Tsuji and his coworkers laid the groundwork for a multitude of useful processes which 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. In addition to quaternary centers, several examples of the synthesis of tertiary stereocenters have been reported. The versatility of these methods provide 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 [49]) are indicative of the ongoing legacy of these contributions. The authors anticipate a multitude of future reports on the utility of these reactions that will further demonstate the importance of the pioneering discoveries of Prof. Tsuji.

Acknowledgments

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Biographies

Brian M. Stoltz was born in Philadelphia, Pennsylvania, USA in 1970. After spending a year at the Ludwig Maximilians Universität in München, Germany, he obtained his B. S. in Chemistry and B. A. in German from Indiana University of Pennsylvania in 1993. He then earned his Ph. D. in 1997 under the direction of Professor John L. Wood at Yale University. Following an NIH postdoctoral fellowship in the laboratories of Professor E. J. Corey at Harvard University (1998-2000), he joined the faculty at Caltech in 2000 and is currently a Professor of Chemistry. His research focuses on the design and implementation of new synthetic strategies for the synthesis of complex molecules possessing important biological properties and the development of new synthetic methods including asymmetric catalysis and cascade processes.

Justin T. Mohr was born in Anchorage, Alaska, USA in 1980. He received his A. B. degree in chemistry from Dartmouth College in 2003, where he worked in the labs of Professor Gordon W. Gribble. He has worked toward a Ph. D. in the labs of Professor 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 synthesis of structurally and biologically interesting molecules.

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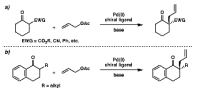
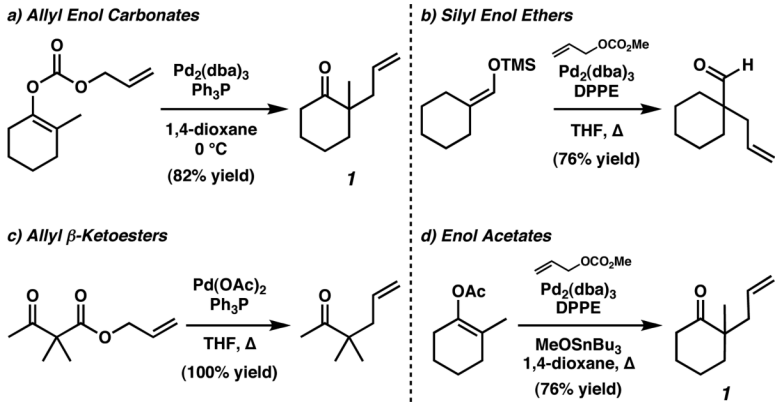
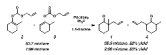


Scheme 1.

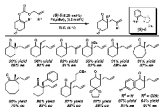
a) Enantioselective allylic alkylation with stabilized enolates. b) Enantioselective allylic alkylation with unstabilized enolates.



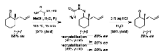
Scheme 2.
Tsuji allylation reactions. (dba = dibenzylideneacetone; TMS = trimethylsilyl; DPPE = bis (diphenylphosphino)ethane)



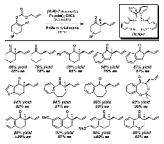
Scheme 3.
Regiochemical fidelity in the Tsuji allylation.



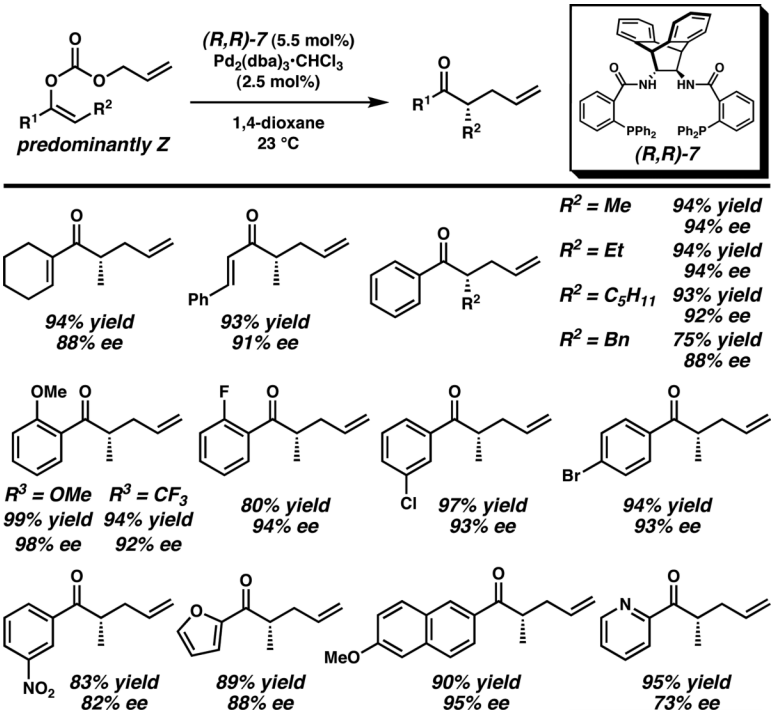
Scheme 4.
Enantioenriched cycloalkanones produced from allyl enol carbonates.



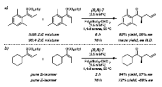
Scheme 5.
Enantioenrichment of ketone (–)-**1** via the semicarbazone derivative.



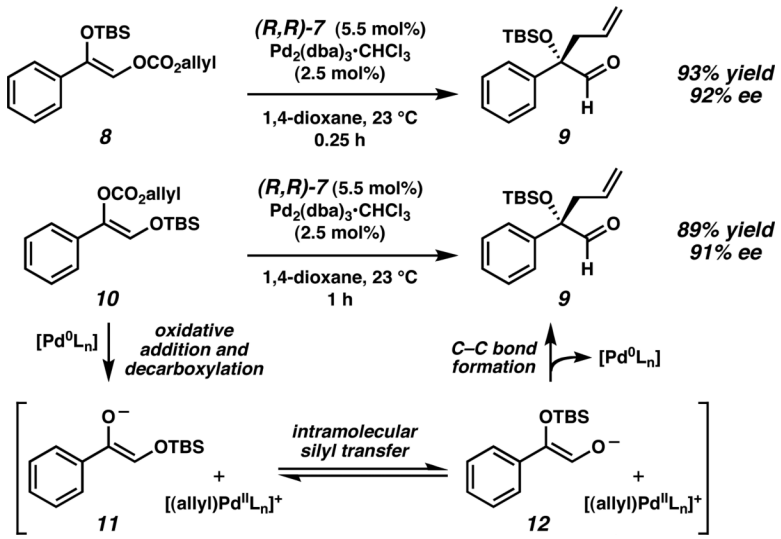
Scheme 6.
Enantioenriched cycloalkanones produced from allyl enol carbonates.



Scheme 7.
Enantioenriched ketones produced from (Z)-enol carbonates.

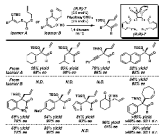


Scheme 8.
Reactivity differences for (*E*)- and (*Z*)-enol carbonates. (N.D. = not determined)

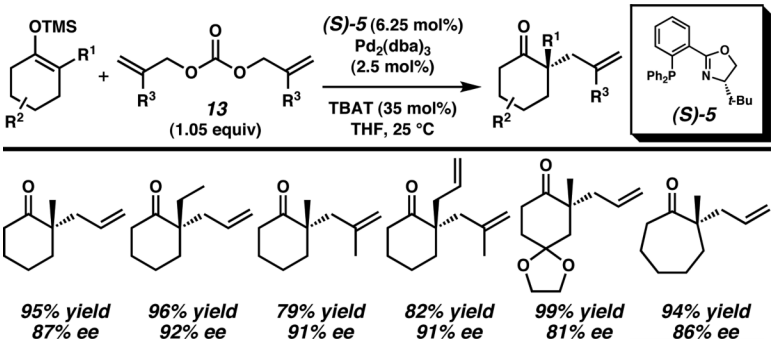


Scheme 9.

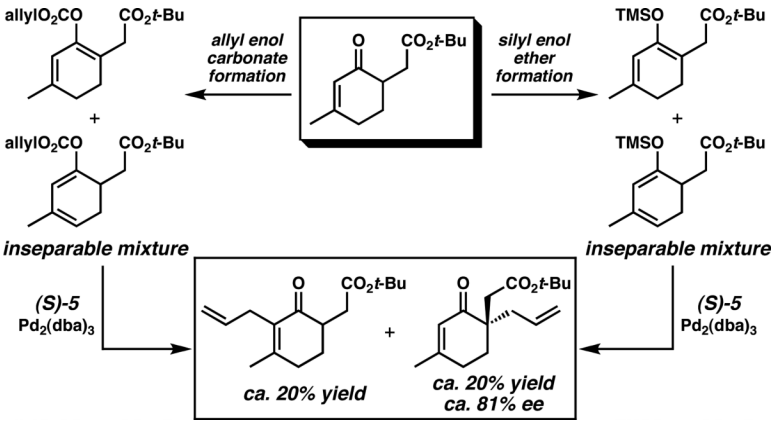
Allylic alkylation from isomeric silyloxy substituted allyl enol carbonates. (TBS = *tert*-butyldimethylsilyl)



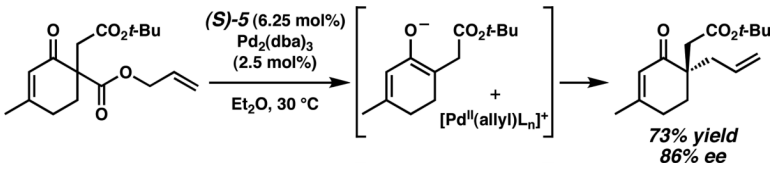
Scheme 10.
Allylic alkylation to form α-silyloxy aldehydes and ketones.



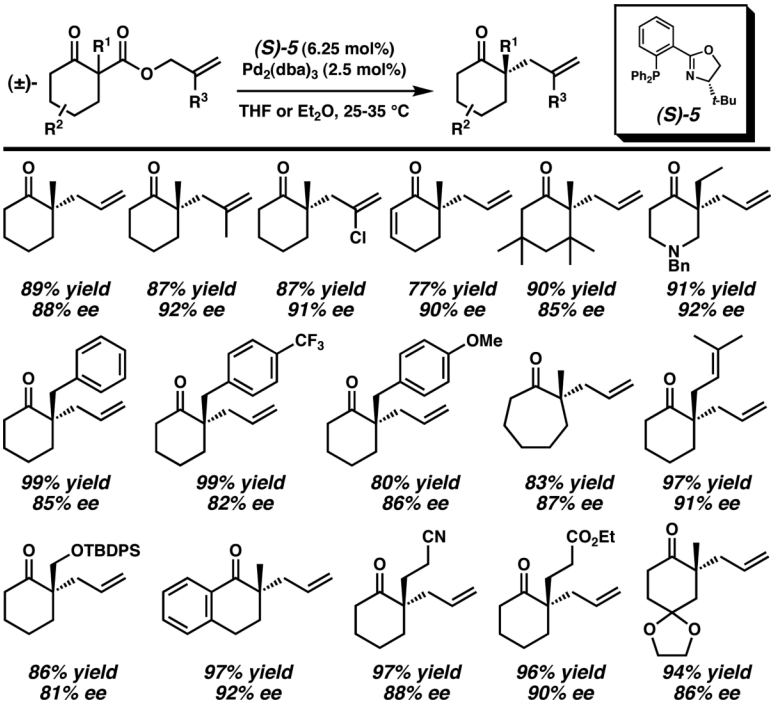
Scheme 11.
Enantioenriched cycloalkanones produced from silyl enol ethers.



Scheme 12.
Non-selective enolization leads to mixtures of allylated products.

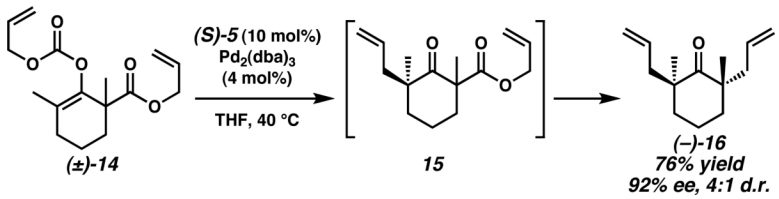


Scheme 13.
Enantioselective decarboxylative allylation with an allyl β-ketoester.

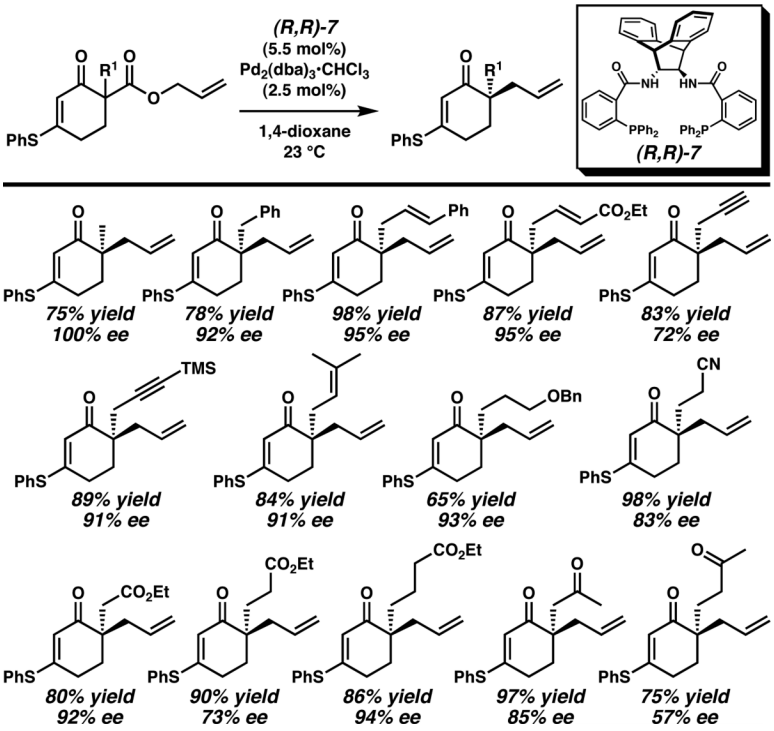


Scheme 14.

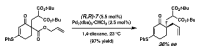
Enantioenriched cycloalkanones prepared from allyl β-ketoesters. (TBDPS = *tert*-butyldiphenylsilyl)



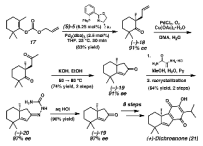
Scheme 15.
Enantioselective cascade allylation generating two quaternary stereocenters.



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

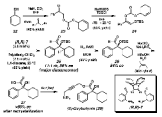


Scheme 17.
Allylation in the presence of a pendent 1,3-diester.

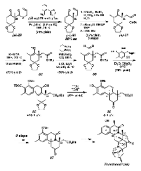


Scheme 18.

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

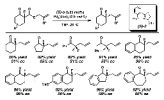


Scheme 19.
Enantioselective formal synthesis of (*S*)-oxybutynin. (HMDS = hexamethyldisilazane)

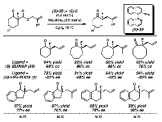


Scheme 20.

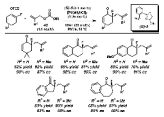
Progress toward the total synthesis of zoanthenol. (Boc = *tert*-butyloxycarbonyl; DMAP = 4-(dimethylamino)pyridine; LDA = lithium diisoproylamide; Tf = trifluoromethanesulfonyl; Cy = cyclohexyl; TBAF = tetrabutylammonium fluoride)



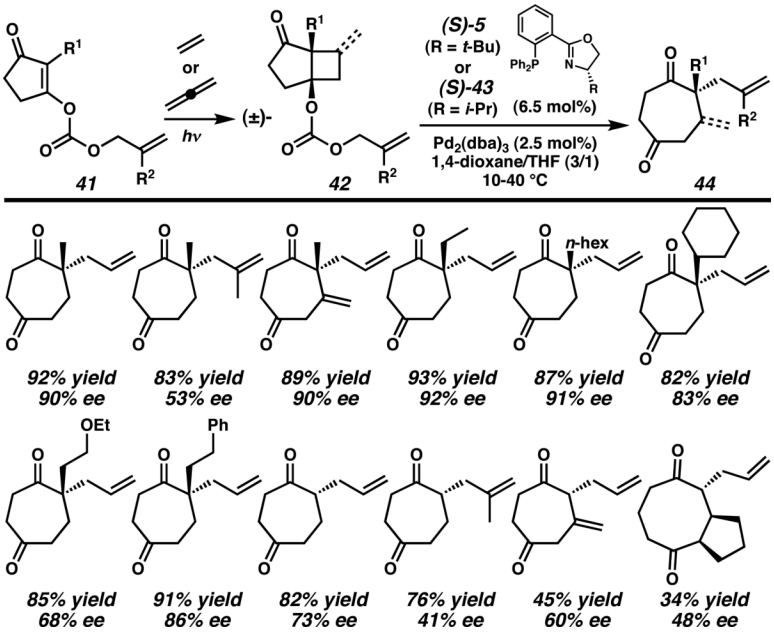
Scheme 21.
Enantioenriched α-fluoroketones derived from allyl β-ketoesters.



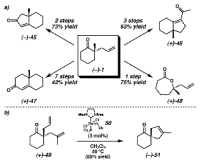
Scheme 22.
Enantioenriched α-fluorocycloalkanones prepared from allyl β-ketoesters. (N.D. = not determined)



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

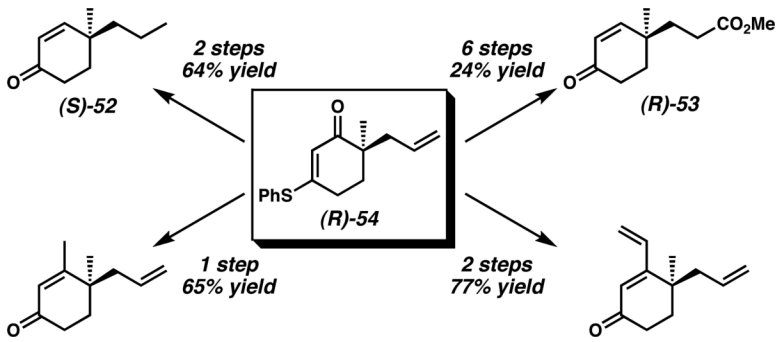


Scheme 24.
Asymmetric ring-expanding allylation.

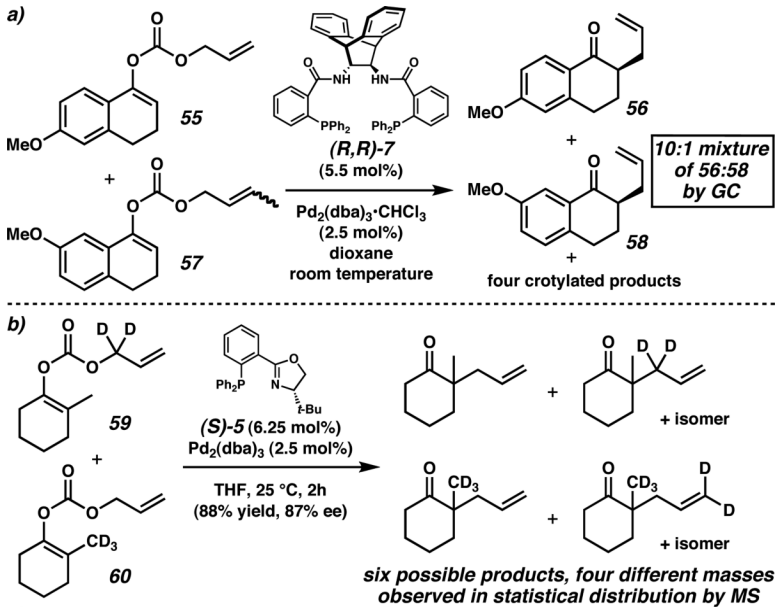


Scheme 25.

a) Transformations of ketone (–)-**1**. b) Ring closing metathesis generating a spirocycle.

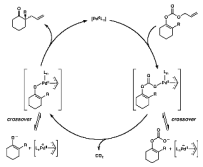


Scheme 26.
Stork-Danheiser type transformations of vinylogous thioester (*R*)-**51**.



Scheme 27.

a) Trost's crossover experiment. b) Stoltz' crossover experiment.



Scheme 28.
Possible catalytic cycle for decarboxylative allylation.