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Catalytic Enantioselective Alkylation of Prochiral Ketone Enolates

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Background

The synthesis of stereogenic all-carbon quaternary centers remains a formidable challenge, notwithstanding the strides made by modern organic chemistry in this regard [1]. Contemporary advances in enolate alkylation have made it a fundamental strategy for the construction of C–C bonds [2]. Although methods for the reaction of a number of enolate types (e.g., ester, ketone, and propionimide) with a variety of alkylating agents exist, catalytic enantioselective variants of these transformations are relatively rare [3]. Of the catalytic asymmetric methods available, there have been few examples of general techniques for the asymmetric alkylation of carbocyclic systems and still fewer examples that have the capacity to deliver all-carbon quaternary stereocenters [4]. While the Merck phase transfer methylation and Koga alkylation of 2-alkyltetralone-derived silyl enol ethers represent notable exceptions [4], the breadth of application and utility of these reactions has been limited. In fact, at the outset of our investigations in this area, there were no examples of catalytic enantioselective alkylations of monocyclic 2-substituted cycloalkanone enolates in the absence of either α′-blocking groups or α-enolate-stabilizing groups (e.g., R = aryl, ester, etc.; Figure 1). Concurrent to our work in this area, Trost and coworkers [5] have published a series of papers that complement our studies. Jacobsen and coworkers, as well, have revealed a unique enantioselective method involving the chromium-catalyzed reaction of tin enolates with a variety of unactivated alkyl halides [4a]. Herein, we relate our development of Pd-catalyzed enantioselective functionalization reactions of prochiral enolates, specifically tetrasubstituted cyclic ketone enolates that give rise to quaternary stereogenicity [6]. The synthetic utility of the building blocks derived from these reactions is demonstrated by application in a number of total syntheses.

Strategy and Results

In 2003, we initiated a program aimed at the catalytic enantioselective synthesis of all-carbon quaternary stereocenters by allylic alkylation of prochiral cyclic ketone

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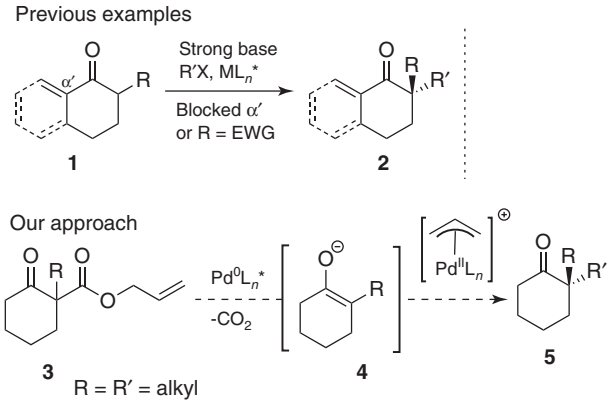
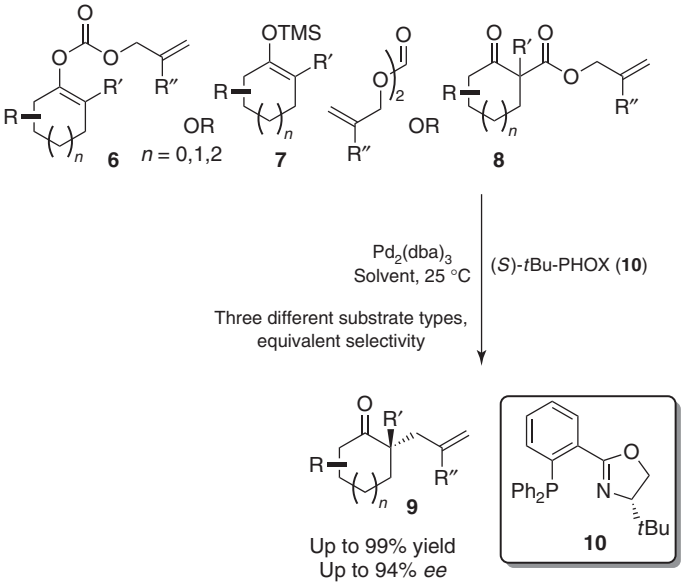


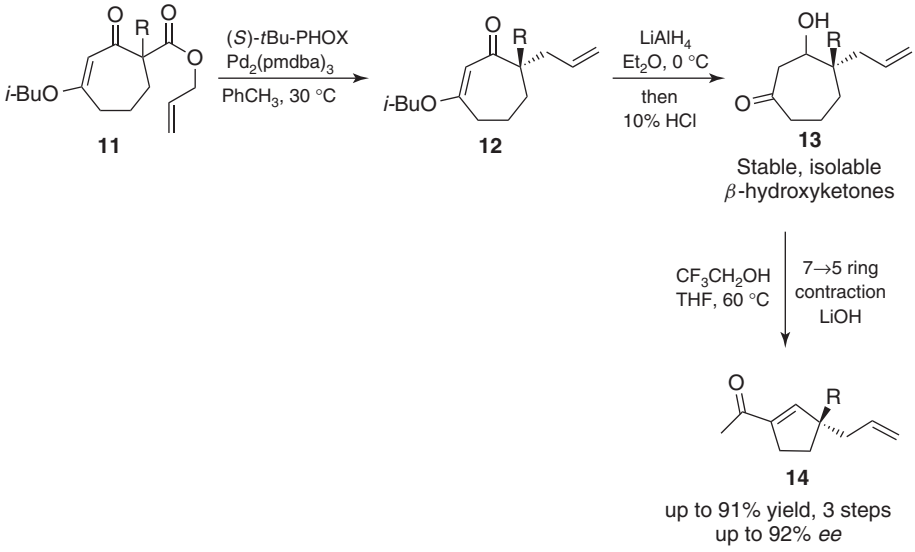
Figure 1 Enolate reactions: previous examples and our approach.



Scheme 1 Enantioselective alkylation methodology.

enolates [6]. We adapted a protocol originally developed by Tsuji and Minami [7] to incorporate a chiral ligand scaffold and found that the phosphinooxazoline (PHOX) ligands (e.g., **10**) [8] were optimal for both chemical yields and enantioselectivity. The allylic alkylation protocol that we developed was robust enough to employ several different enolate precursors as substrates, namely, allyl enol carbonates (**6**), enol silanes (**7**), and β-ketoesters (**8**; Scheme 1) [6].

In addition, the reaction is highly tolerant of a broad range of functionality and substitution on both the enolate precursors and allyl fragments. Enolates derived from cyclic ketones [4], enones [4], vinylogous esters [9], vinylogous thioesters



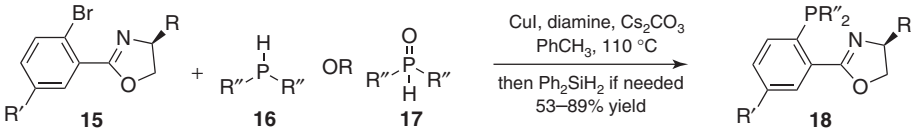
Scheme 2 Ring contraction methodology.

[10], tetralones [4], and dioxanones [11] function with similar levels of selectivity in the catalytic asymmetric chemistry. We have also developed a highly efficient large-scale protocol that employs reduced catalyst loading (2.5 mol% Pd) and allows access to greater than 10 of enantioenriched material.

Furthermore, we have been able to exploit seven-membered ring vinylogous ester substrates (**11**) by virtue of a unique trait that these molecules possess in contrast to their six-membered counterparts. While cyclohexanone products will readily eliminate to form cyclic enones under Stork–Danheiser conditions (reduction and treatment with acid) [13], cycloheptanones (**12**) form stable β-hydroxy ketone intermediates (**13**). Our efforts have uncovered a retro-aldol/aldol ring contraction strategy to access a number of functionalized acyl cyclopentenes (**14**) from this unusual and unexpected product [14] (Scheme 2).

In addition to the desirable properties of (*S*)-*t*Bu-PHOX (**10**), the PHOX ligand scaffold was found to be highly modular, such that a range of steric and electronic properties could be investigated [15]. Our studies in this area were facilitated by the use of a copper-catalyzed coupling reaction of aryl halides (**15**) and phosphines (**16**) or phosphine oxides (**17**), originally developed by Buchwald [16] (Scheme 3). As with our enantioselective reaction itself, production of the ligand on a large scale is also feasible [17].

We have intensely investigated the mechanism of these alkylation reactions in an effort to understand the elements controlling asymmetric induction so that we may design catalysts with greater reactivity and enantioselectivity. An intriguing picture of the general reaction mechanism has emerged from our experimental studies. Preliminary kinetics experiments demonstrate that the reactions are first order with respect to [Pd · PHOX] and zeroth order with respect to [substrate]. Furthermore,



Scheme 3 Concise, scalable synthesis of phosphinooxazoline (PHOX) ligands.

we have carried out Kagan-type nonlinear effect experiments and found a linear relationship between the enantiomeric excess of ligand and product [18]. Finally, we have been using NMR spectroscopy and single crystal X-ray analysis to characterize intermediates and resting states in the catalytic cycle [19].

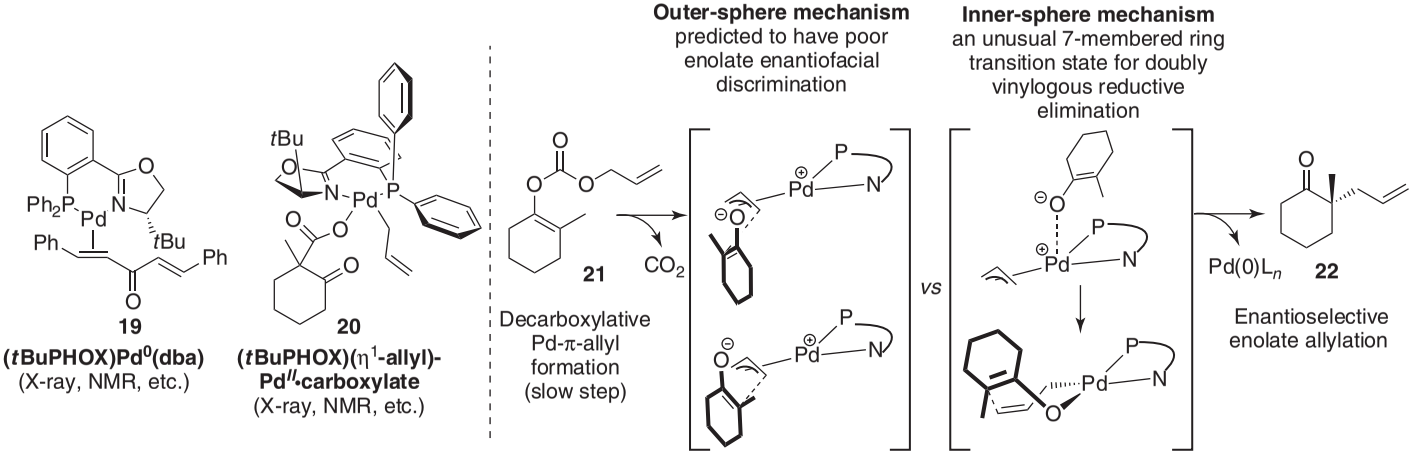
We have confirmed that adduct **19**, with an η^2-coordinated dba ligand [20], is initially formed, but that in the presence of substrate, a highly unusual η^1-allyl, η^1-carboxylate Pd · PHOX complex (**20**) persists (Scheme 4) [21]. These complexes are the resting states of the catalytic cycle, depending on whether substrate is available (**20**) or not (**19**) and point to decarboxylation as the slow step of the catalytic cycle [19]. Because the enantiodetermining step is kinetically inaccessible to direct observation, we turned to computational modeling, in collaboration with Professor William Goddard at Caltech, to investigate the possible transition states for the allylation. While it is still premature to draw definitive conclusions, it appears that an inner-sphere mechanism is operative wherein attack of the derived enolate occurs first on Pd, followed by a reductive elimination pathway to produce the C–C bond (Scheme 4) [22].

Although this mechanistic hypothesis contrasts the accepted mechanism for most asymmetric allylic alkylations (i.e., outer-sphere backside attack on the π-allyl-Pd complex) [23], an inner-sphere mechanism would more reasonably account for the high enolate enantiofacial preference and for the limitations on the size and substitution of the allylic fragment. Furthermore, reactions involving stabilized enolates (Scheme 1, R = aryl, CO_2R, etc.) lead to low enantioselectivity under our conditions, pointing to the possibility of a mechanistic switch between inner-sphere (high selectivity) and outer-sphere (low selectivity) pathways depending on the substrate electronics.

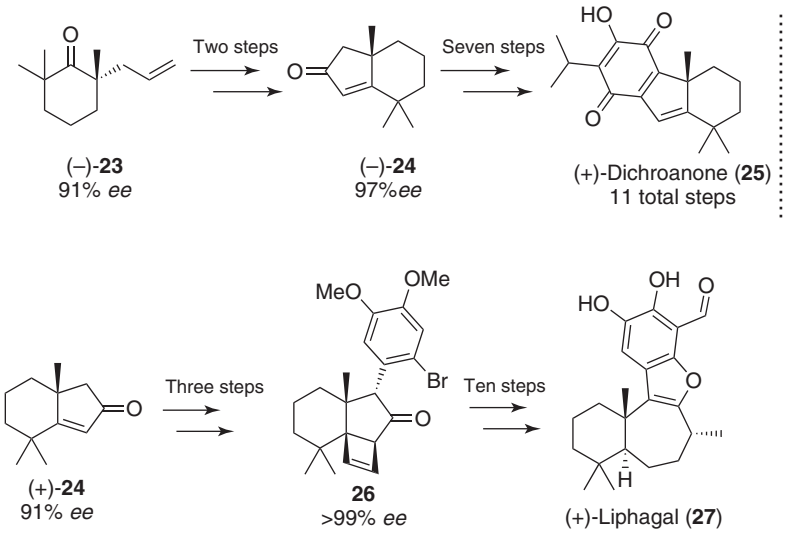
In view of our mechanistic findings, we hypothesized potential interception of our putative chiral metal enolate species and subsequent trapping with alternative electrophiles. Indeed, via acidic trapping, we are able to generate an array of chiral α-tertiary cycloalkanones in high yield and enantioselectivity [24]. Benzylidene-malononitrile-derived conjugate acceptors may be coupled along with an allyl cation fragment to deliver highly functionalized, vicinal all-carbon quaternary and tertiary stereocenters neighboring an achiral quaternary center in good diastereo- and enantioselectivities [25].

Asymmetric Allylic Alkylation in Total Synthesis

Quaternary centers are present in thousands of natural products and are especially prominent in large numbers of terpenes and bioactive alkaloids [26]. The



Scheme 4 Isolated intermediates and comparison of inner- and outer-sphere pathways.



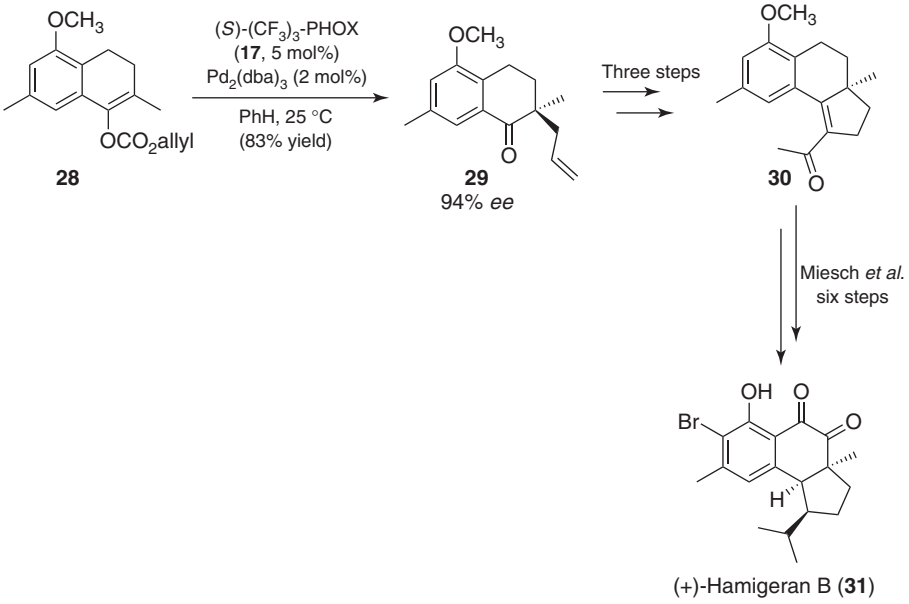
Scheme 5 Total syntheses of (+)-dichroanone and (+)-liphagal.

α-quaternary cycloalkanones produced by our asymmetric alkylation chemistry are highly useful chiral building blocks, containing at least two functional groups, a ketone and an olefin, for further manipulation. We have prepared a number of natural products by employing our technology as a critical means to build structural complexity and set absolute stereochemistry.

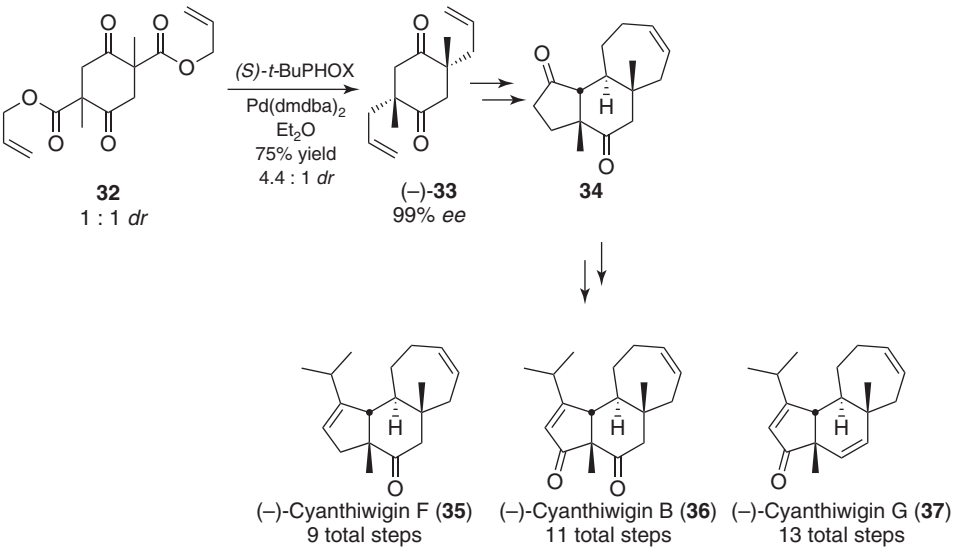
Our early efforts resulted in a rapid, protecting-group-free synthesis of (+)-dichroanone (**25**) via the intermediacy of bicyclic enone (**24**), a compound accessible by a two-step sequence from alkylation product **23** (Scheme 5) [27]. In addition, enone (**24**) could be recrystallized via the semicarbazone derivative to 97% *ee*. This same intermediate (**24**), in the enantiomeric series, was recently employed in the total synthesis of (+)-liphagal (**27**) [28–30]. Our unique synthesis [31] allows access to a variety of structural and functional liphagal congeners.

An enol carbonate substrate (**28**) was employed in the expedient formal synthesis of (+)-hamigeran B (**31**; Scheme 6) [32, 33]. Our approach rapidly builds the tricyclic core (**33**) in a highly enantioselective manner and ties into the Miesch synthesis of racemic hamigeran B [34], leading to enantioenriched hamigeran B (**31**) in only 10 steps from carbonate (**28**).

In an effort to construct both quaternary stereocenters present in the cyathane diterpenoid natural products [35, 36] in a single transformation, we designed bis(β-ketoester) (**32**), which was employed in a stereoconvergent process that converted each of the three stereoisomeric starting materials (i.e., two C_2 symmetric enantiomers and one meso diastereomer) to an enantioenriched product with excellent and amplified stereocontrol (e.g., **32** → **33**; Scheme 7) [37]. The successful application of this double enantioselective decarboxylative allylation strategy led to the rapid total synthesis of cyanthiwigin F (**35**), as well as cyanthiwigins B (**36**) and G (**37**) [38].



Scheme 6 Formal synthesis of (+)-hamigeran B.



Scheme 7 Total synthesis of (−)-cyanthiwigins F, B, and G.

Conclusions

We have developed an allylic alkylation reaction for the assembly of enantioenriched α-quaternary carbonyl compounds. This methodology has enabled the rapid construction of a number of natural products that feature all-carbon quaternary centers. In addition to cyclic ketones, we have expanded our asymmetric alkylation reaction substrate scope to include lactams, which undergo the chemistry in excellent yield and enantioselectivities [39]. Expansion of scope of this method and its application in total synthesis are ongoing areas of research in our group.

CV of Corey M. Reeves

Corey M. Reeves was born in Santa Monica, CA, USA. Corey obtained a BS in Chemistry and BA in Sociology from Columbia University in New York City in 2009. During this time, he completed undergraduate research under the guidance of Professor Tristan Lambert. In 2010, he began doctoral studies at the California Institute of Technology, working in the laboratory of Professor Brian Stoltz.

CV of Brian M. Stoltz

Brian M. Stoltz was born in Philadelphia, PA, USA, in 1970. After spending a year at the Ludwig Maximilians Universität in München, Germany, he obtained his BS in Chemistry and BA 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 where he is currently the Ethel Wilson Bowles and Robert Bowles Professor of Chemistry and a KAUST GRP Investigator. His research interests lie in the development of new methodology for general applications in synthetic chemistry.

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