



# HHS Public Access

Author manuscript

*Acc Chem Res.* Author manuscript; available in PMC 2019 March 11.

Published in final edited form as:

*Acc Chem Res.* 2015 March 17; 48(3): 740–751. doi:10.1021/ar5004658.

## Catalytic Enantioselective Construction of Quaternary Stereocenters: Assembly of key building blocks for the synthesis of biologically active molecules.

Yiyang Liu, Seo-Jung Han, Wen-Bo Liu, and Brian M. Stoltz\*

The Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering, Division of Chemistry and Chemical Engineering, California Institute of Technology, 1200 East California Boulevard, MC 101-20, Pasadena, California 91125, United States

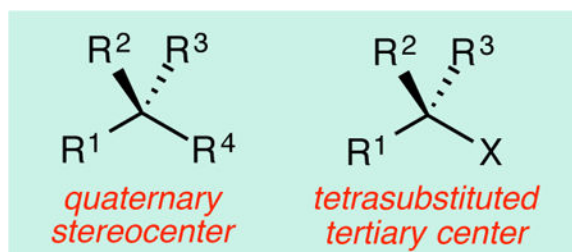
### CONSPECTUS:

The ever-present demand for drugs with better efficacy and fewer side effects continually motivates scientists to explore the vast chemical space. Traditionally, medicinal chemists have focused much attention on achiral or so-called “flat” molecules. More recently, attention has shifted toward molecules with stereogenic centers since their three-dimensional structures represent a much larger fraction of the chemical space and have a number of superior properties compared with flat aromatic compounds. Quaternary stereocenters, in particular, add greatly to the three-dimensionality and novelty of the molecule. Nevertheless, synthetic challenges in building quaternary stereocenters have largely prevented their implementation in drug discovery. The lack of effective and broadly general methods for enantioselective formation of quaternary stereocenters in simple molecular scaffolds has prompted us to investigate new chemistry and develop innovative tools and solutions. In this Account, we describe three approaches to constructing quaternary stereocenters: nucleophilic substitution of 3-haloindoles, conjugate addition of boronic acids to cyclic enones, and allylic alkylation of enolates. In the first approach, malonic ester nucleophiles attack electrophilic 3-halooxindoles, mediated by a copper(II)-bisoxazoline catalyst. A variety of oxindoles containing a benzylic quaternary stereocenter can be accessed through this method. However, it is only applicable to the specialized 3,3-disubstituted oxindole system. To access benzylic quaternary stereocenters in a more general context, we turned our attention to the enantioselective conjugate addition of carbon nucleophiles to  $\alpha,\beta$ -unsaturated carbonyl acceptors. We discovered that in the presence of catalytic palladium-pyridinooxazoline complex, arylboronic acids add smoothly to  $\beta$ -substituted cyclic enones to furnish ketones with a  $\beta$ -benzylic quaternary stereocenter in high yields and enantioselectivities. The reaction is compatible with a wide range of arylboronic acids,  $\beta$ -substituents, and ring sizes. Aside from benzylic quaternary stereocenters, a more challenging motif is a quaternary stereocenter not adjacent to an aromatic group. Such centers represent more general structures in chemical space, but are more difficult to form by asymmetric catalysis. To address this greater challenge, and motivated by the greater reward, we entered the field of palladium-catalyzed asymmetric allylic alkylation of prochiral enolate nucleophiles about a decade ago. On the basis of Tsuji’s work, which solved the issue of positional selectivity for unsymmetrical ketones, we discovered that the

\*Corresponding Author: stoltz@caltech.edu.

phosphinoxazoline ligand effectively rendered this reaction enantioselective. Extensive investigations since then have revealed that the reaction exhibits broad scope and accepts a range of substrate classes, each with its unique advantage in synthetic applications. A diverse array of carbonyl compounds bearing  $\alpha$ -quaternary stereocenters are obtained in excellent yields and enantioselectivities, and more possibilities have yet to be explored. As an alternative to palladium catalysis, we also studied iridium-catalyzed asymmetric allylic alkylations that generate vicinal quaternary and tertiary stereocenters in a single transformation. Overall, these methods provide access to small molecule building blocks with a single quaternary stereocenter, can be applied to various molecular scaffolds, and tolerate a wide range of functional groups. We envision that the chemistry reported in this Account will be increasingly useful in drug discovery and design.

## Graphical Abstract



## 1. Introduction

As humanity settles into the second decade of the 21<sup>st</sup> Century, science continues to press forward with new advances that alter our experiences on a daily basis. The fields of medicinal and pharmaceutical chemistry are no different, with new medicines becoming available to treat the most threatening and problematic maladies of the day. Although the landscape of drug discovery and the pharmaceutical industry continue to change, particularly with the vibrant increase in new types of large molecule medicinal agents, small molecule chemistry is likely to continue to play a critical role in the discovery of new active pharmaceutical ingredients (API) well into the future. Therefore, it is critical that academic chemists continue to develop thoughtful strategies, implement sound tactical maneuvers, and invent robust new technologies for the synthesis of biologically rich, complex small molecules that will allow medicinal chemists to explore new molecular space with functional compounds having better properties.

For many years, medicinal chemists have focused attention on achiral aromatic and heteroaromatic molecules as potential drug candidates.<sup>1</sup> This is in part due to the relative ease of their preparation, especially since the emergence of cross-coupling chemistries and parallel synthesis, and their biased population in screening suites at most companies. While many of such compounds have been developed into successful drugs, their lack of stereochemistry presents a number of drawbacks at a fundamental level. First, achiral or “flat” molecules occupy only a small fraction of chemical space. From a structural diversity perspective, a vast number of possibilities have not been explored. Second, the two-dimensional nature of aromatic molecules implies that their interaction with target proteins, which have a three-dimensional structure, will be limited. Therefore, high selectivity for

binding to the desired protein (for instance) over undesired ones is difficult to achieve, and side effects such as cytotoxicity often pose a challenge. Finally, polyaromatic molecules tend to interact strongly with one another due to  $\pi$ -stacking, thereby resulting in low solubility and poor bioavailability.

A promising solution to the issues raised above is to incorporate  $sp^3$ -hybridized carbon stereocenters into the molecule. This topic has been the subject of recent review articles and essays.<sup>2</sup> In particular, quaternary stereocenters, which bear four different carbon substituents at the four vertices of a tetrahedron, add greatly to the three-dimensionality of a molecule. However, construction of quaternary stereocenters via chemical synthesis is extremely challenging.<sup>3</sup> While 21 compounds out of the top 200 drugs by US retail sales in 2012<sup>4</sup> have quaternary stereocenters (>10%, examples shown in Figure 1), all of those structures are derived from natural products. These include terpenoid (**1–5** and **9**) and morphine (**6–8**) derivatives, where the quaternary stereocenters are made by nature and the API is typically produced by peripheral derivatization. *Within those 200 top pharmaceuticals, none have a quaternary stereocenter built by chemical synthesis.* This dichotomy reflects the paucity of synthetic methods available for the construction of quaternary stereocenters and consequently the lack of their applications in drug discovery.

Traditional chemical approaches to quaternary stereocenters include the Claisen rearrangement<sup>5</sup> and the Diels–Alder reaction.<sup>6</sup> While these reactions are well established, the formation of the quaternary stereocenter is often accompanied by formation of other stereocenters nearby. From a drug discovery perspective, this potentially introduces unnecessary complexity, collaterally obscuring structure-activity relationship (SAR) studies. Construction of a single quaternary stereocenter in a simple molecular scaffold is much more desirable. Most critical would be to develop robust methods that allow one to perform rigorous SAR studies while maintaining the quaternary center as a constant.

During the past decade, our research group has strategically tackled this problem by implementing an array of orthogonal approaches. The most well studied tactics that have emerged from our laboratories involve the alkylation of 3-haloindole electrophiles, the conjugate addition of boronic acids to cyclic enones, and the allylic alkylation of enolates. In all three approaches, we have achieved catalytic asymmetric construction of quaternary stereocenters in high yield and enantioselectivity with broad substrate scope. We believe that these methods will greatly expand the medicinal chemist's synthetic toolbox and facilitate access to potential drug candidates containing quaternary stereocenters.

## 2. Enantioselective syntheses of C(3) all carbon quaternary centers on oxindoles by alkylation of 3-bromooxindoles

3,3-Disubstituted oxindoles and their derivatives are widely encountered in numerous biologically active natural products<sup>7</sup> and pharmaceutical compounds.<sup>8</sup> A considerable amount of effort has thus been devoted toward the construction of 3,3-disubstituted oxindoles over the past decade.<sup>9,10</sup> However, a non-traditional use of the oxindole core as an electrophile rather than as a nucleophile toward the catalytic enantioselective generation of C(3) quaternary substituted oxindoles was unprecedented and discovered by our laboratory.

In 2007, we reported a method for the construction of 3,3-disubstituted oxindoles in good yields by alkylation of malonate nucleophiles with 3-halooxindoles as electrophiles, presumably via indolones **11** (Scheme 1A).<sup>11</sup> Additionally, by employing these mild conditions, we could access the core structures of the complex polycyclic alkaloid natural products communesin F (**19**) and perophoramidine (**20**, Scheme 1B).<sup>12</sup> In view of these promising results, we turned our attention to the asymmetric synthesis of C(3) all-carbon quaternary substituted oxindoles.<sup>13</sup> We envisioned that employing a chiral Lewis acid catalyst would facilitate an asymmetric variant of our alkylation reactions under mild basic conditions. Gratifyingly, we found that smooth enantioselective alkylation of 3-bromooxindole by malonates was achieved in good yields and high enantioselectivities by implementing a chiral Cu•BOX catalyst with a weakly coordinating counter ion such as SbF<sub>6</sub> (Table 1). A variety of substituted alkyl chain lengths were tolerated in the chemistry, as were numerous functional groups. Additionally, 3-aryl-3-chlorooxindoles were also alkylated to produce the corresponding 3,3-disubstituted oxindoles in good yields and high enantioselectivities. Our method stands as one of the only that allows the preparation of both C3-alkyl and C3-aryl quaternary oxindoles with a single catalyst system.

Mechanistically, we envision that prochiral indolone **11** is likely to be an intermediate, since racemic starting materials remain throughout the course of the reaction and are converted to products of high ee (Scheme 2A), and alkylation reactions employing *N*-Me oxindole **21** as electrophiles are unsuccessful under our standard conditions (Scheme 2B).

### 3. Palladium-catalyzed asymmetric conjugate addition of arylboronic acids to cyclic enones to furnish benzylic quaternary centers

Although the alkylation of malonate nucleophiles to halooxindoles produces a quaternary benzylic carbon stereocenter, it does so in a very specialized system, the 3,3-disubstituted oxindole series. In order to produce benzylic quaternary centers in a more general way, we turned to the catalytic asymmetric conjugate addition of a carbon-based nucleophiles to  $\beta$ -substituted  $\alpha,\beta$ -unsaturated carbonyl acceptors.<sup>14</sup> For transition metal approaches, there have been two successful major catalytic systems, copper and rhodium. To date, most nucleophiles employed in copper-catalyzed conjugate additions are highly reactive organometallic species such as diorganozinc,<sup>15</sup> triorganoaluminum,<sup>16</sup> and organomagnesium reagents.<sup>17</sup> The air- and moisture-sensitive nature of these nucleophiles requires strictly anhydrous reaction conditions. On the other hand, air-stable organoboron reagents have been used in rhodium-catalyzed conjugate additions,<sup>18</sup> although there are relatively few examples of quaternary stereocenter formation.<sup>19</sup> In one report, it was shown that sodium tetraarylborates and arylboroxines could add to  $\beta,\beta$ -disubstituted enones to deliver  $\beta$ -quaternary ketones.<sup>20</sup> From a practical standpoint, using commercially available arylboronic acids as nucleophiles will make conjugate addition a much more valuable method for quaternary stereocenter generation. Additionally, the ultra-high cost of Rhodium can often be prohibitive. As a remedy for these substantial hurdles, we embarked on a program to develop Pd catalysts that could be employed with aryl boronic acids for this purpose.

Palladium-catalyzed conjugate addition of arylboronic acids to enones has been widely studied and has led to development of addition reactions that form enantioenriched tertiary stereocenters.<sup>21</sup> More recently, Lu reported a bipyridine-palladium complex-catalyzed conjugate addition to form quaternary stereocenters in racemic form.<sup>22</sup> We envisioned that by using chiral ligands, enantioselective formation of quaternary stereocenters might be achieved.<sup>23</sup> With 3-methyl-2-cyclohexenone and phenylboronic acid as model reactants, we examined a range of reaction parameters, and discovered that a combination of easily accessible chiral pyridinooxazo-line (PyOx) ligand, a commercial palladium(II) trifluoroacetate precatalyst, and 1,2-dichloroethane as solvent provided the desired  $\beta$ -quaternary ketone in high yield and excellent ee. Notably, the reaction was not sensitive to oxygen or moisture, and thus could be performed under ambient atmosphere without the need for anhydrous solvents.

With the optimal conditions in hand, we explored the substrate scope of palladium-catalyzed conjugate addition of arylboronic acids to cyclic enones (Table 2). In addition to a variety of substituents on the aromatic ring of the boronic acid, 5-, 6-, and 7-membered cyclic enones are all competent substrates for the reaction. Enones bearing more complex substituents at the  $\beta$ -position also undergo conjugate addition smoothly to afford the corresponding  $\beta$ -quaternary ketones in good yields and good to high ee.

During scale-up studies, we found that addition of water was necessary for the complete conversion of starting material (Scheme 3). With 5 equiv of water, a 22 mmol scale reaction proceeded smoothly to furnish 3-methyl-3-phenylcyclohexanone (**33**) in 97% yield and 91% ee. Further investigation revealed that addition of water and ammonium hexafluorophosphate had a synergistic effect in increasing reaction rate. Thus, more challenging substrates such as *ortho*-substituted arylboronic acid could also be employed in conjugate addition to give the desired products in much better yields compared with the previous conditions (Table 3).<sup>24</sup>

Finally, a series of experimental and computational mechanistic studies revealed that a likely mechanistic path for the reaction is shown in Scheme 4.<sup>24</sup> The catalytic cycle consists of transmetalation from boron to palladium, insertion of the enone substrate into the arylmetal bond, and protonolysis of the resulting palladium-enolate **30**. These investigations suggest that the bond-forming palladium species is an arylpalladium(II) cation (**28**), and enantioselectivity is governed by steric repulsions between the *t*-Bu group of the chiral ligand and the  $\alpha$ -methylene hydrogens of the cyclohexenone substrate.

#### 4. Palladium-Catalyzed Enantioselective Allylic Alkylation of Prochiral Enolates

The first two sections of this manuscript discuss benzylic quaternary centers, yet a potentially greater challenge to asymmetric catalysis lies in bond forming chemistries that have no proximal aromatic groups. It is often the case that asymmetric reactions may function at benzylic positions and then fail upon extension to the alkyl variant. For the construction of quaternary centers, the case is no different. It was precisely this limitation,

and our concomitant efforts in the context of a multi-step synthesis, that guided our entry into this entire field, more than a decade ago.<sup>25</sup>

Palladium-catalyzed asymmetric allylic alkylation is a powerful C–C bond forming process that allows for the construction of stereogenic centers.<sup>26</sup> A typical catalytic cycle involves the oxidative generation of a  $\pi$ -allylpalladium intermediate from an allyl electrophile, followed by nucleophilic attack on the allyl terminus, resulting in reduction of the metal center (Scheme 5). The pioneering earlier works of Trost,<sup>27</sup> Helmchen,<sup>28</sup> and others focused mainly on prochiral allyl electrophiles. Although this reaction mode enjoys success with a broad range of substrates and has found numerous applications in natural products synthesis, it typically produces only tertiary stereocenters. Formation of quaternary stereocenters by C-nucleophilic addition to prochiral allyl electrophiles has been carried out with other metals, such as copper.<sup>29</sup>

Another mode of reactivity makes use of a prochiral nucleophile. A quaternary stereocenter may be formed if the nucleophile possesses three distinct substituents. One typical example of such nucleophiles is a tetrasubstituted enolate, generated by deprotonation of a carbonyl compound. However, position-selective enolate generation can be particularly challenging if the carbonyl compound bears multiple, similarly acidic  $\alpha$ -protons. For example, deprotonation and alkylation of nonsymmetrical ketones generally lead to an intractable mixture of positional isomers (Scheme 6A). To address this selectivity issue, two strategies have been classically pursued. One of them installs a blocking group at the undesired  $\alpha$ -position (Scheme 6B).<sup>30</sup> The other strategy introduces an electron-withdrawing group at one of the  $\alpha$ -positions to dramatically lower its *pKa* and stabilize the enolate thus formed (Scheme 6C).<sup>31</sup> Although these tactics circumvent the positional selectivity problem, they require additional functional groups that potentially need removal or manipulation, thus reducing overall efficiency and synthetic utility.

We were drawn to the pioneering work of Tsuji to provide an alternative solution to this position selectivity problem in the context of enantioselective catalysis. In the early 1980s, the Tsuji group reported the non-enantioselective allylic alkylation of silyl enol ethers, enol carbonates, and  $\beta$ -ketoesters derived from nonsymmetrical, nonstabilized ketones, in the presence of catalytic palladium and phosphine ligand (Scheme 7).<sup>32</sup> The first substrate class involves separate nucleophiles and electrophiles (Scheme 7A), while the other two classes build the latent enolate nucleophile and the allyl electrophile into one molecule (Scheme 7B and C). The Tsuji allylic alkylation furnishes simple  $\alpha$ -quaternary ketones with high positional fidelity, and the reaction proceeds under mild and nearly neutral conditions, with no exogenous base required. Despite these important advantages, the Tsuji allylic alkylation saw little application in organic synthesis for two decades and no asymmetric version was known until our first report in 2004.<sup>33</sup>

We became interested in developing an enantioselective variant of the Tsuji allylic alkylation because of its regiochemical fidelity and the synthetic utility of its products. We envisioned that a chiral phosphine ligand might impart asymmetric induction in the reaction, leading to preferential formation of one of the enantiomers. With allyl enol carbonate **33** as substrate, we examined a number of chiral bidentate phosphine ligands of various scaffolds and

different chelating atoms and were pleased to discover that the phosphinooxazoline ligand (*S*)-*t*-Bu-PHOX (**36**) provided excellent reactivity and high enantioselectivity (96% yield, 88% ee; see Scheme 8).

Since this initial discovery, we have intensely investigated the scope of this catalysis and found it to be extensive. From a practical standpoint, an important finding was our ability to initiate the chemistry starting from a range of substrate classes. Specifically, in addition to the prototypical enol allyl carbonate, silyl enol ethers, allyl  $\beta$ -ketoesters, allyl enol ethers, and trimethyl silyl ethyl keto esters can serve as nearly equivalent masked enolate substrates (Figure 2). The electrophilic allyl unit can bear carbonates, acetates, sulphonates, and in some instances even halides as the leaving group. The great flexibility in substrate choice allows for strategic implementation in the context of multi-step synthesis, with each substrate class engendering different and unique tactical advantages.

A wide array of quaternary ketones with various scaffolds and substituents can be accessed through our allylic alkylation chemistry with high yield and enantioselectivity (Table 4).<sup>33,34</sup> Substitutions at the  $\alpha$ -position, the 2-allyl position, and on the ring are all well tolerated. Substrates with seven- and eight-membered rings undergo the alkylation reaction smoothly. In addition to quaternary stereocenters, fully substituted tertiary centers can also be built by the reaction.<sup>35</sup>

During our investigations, we became aware of the ligand electronic effects on reaction rate and selectivity. In many cases, the electron-deficient phosphinooxazoline ligand (*S*)-(CF<sub>3</sub>)<sub>3</sub>-*t*-Bu-PHOX (**37**, Table 5) lead to faster reaction rates and higher enantioselectivities, as compared with the standard (*S*)-*t*-Bu-PHOX ligand. This modification of ligand electronics allowed us to improve the reaction's performance with more challenging classes of substrates such as cyclobutanones<sup>36</sup> and lactams.<sup>37</sup> Fully substituted tertiary carbonyl compounds, such as morpholinones,<sup>37</sup>  $\alpha$ -fluorolactams,<sup>37</sup> and piperazines<sup>38</sup> can all be obtained through this chemistry.

A mechanistic rationale has been proposed for the catalytic cycle (Scheme 9). Oxidative addition of Pd(0) to the allyl–O bond of **34** generates complex **39**, which undergoes decarboxylation to form allyl palladium enolate **40**, a key intermediate that can be formed from other starting materials such as silyl enol ether **31** and allyl enol carbonate **33**. Reductive elimination furnishes quaternary ketone product (–)**35** and regenerates the active Pd(0) catalyst **38**.

For the past decade, other labs have also contributed significantly to the field with related methods. Trost reported related palladium-catalyzed asymmetric allylic alkylation using a C<sub>2</sub>-symmetric diamine-based ligand.<sup>39</sup> Nakamura and Paquin each expanded the scope of our method for the enantioselective synthesis of  $\alpha$ -fluoroketones using the Pd/(*S*)-*t*-Bu-PHOX catalyst system.<sup>40</sup> Tunge employed the same catalyst/ligand combination for the decylative allylic alkylation of ketones.<sup>41</sup> The requisite allyl palladium enolate species can also be generated by fragmentation of fused 5–4 ring systems<sup>42</sup> (Scheme 10A) or copper-catalyzed conjugate addition of silanes to enones (Scheme 10B).<sup>43</sup>

Since the reaction involves an enolate nucleophile, we envisioned trapping it with electrophiles other than the allyl fragment. Such electrophiles need to meet two requirements: 1) they do not interfere with oxidative addition or enolate generation; and 2) their reaction with the enolate is faster than direct enolate allylic alkylation. After examination of various carbon electrophiles, we found that arylidenemalononitrile-type Michael acceptors exhibited desired reactivity and produced cyclic ketones bearing adjacent quaternary and tertiary stereocenters (Scheme 11).<sup>44</sup>

## 5. Iridium-Catalyzed Allylic Alkylation for the Construction of Vicinal Quaternary and Tertiary Stereocenters

Based on the intriguing diastereochemical issues encountered in the Pd-enolate trapping chemistry, we became interested in other methods for direct generation of vicinal quaternary-tertiary relationships. Recently, by employing prochiral  $\alpha$ -substituted cyclic  $\beta$ -ketoester enolates as nucleophiles, we developed an Ir-catalyzed direct enantioselective allylic alkylation reaction for the construction of vicinal quaternary-tertiary arrays.<sup>45,46</sup> We explored the reaction with commonly used iridium catalyst systems, derived from  $[\text{Ir}(\text{cod})\text{Cl}]_2$  and phosphoramidite ligands. The catalyst derived from Feringa ligand (**L1**)<sup>47</sup> affords the desired branched product in an equal amount of two diastereoisomers (1:1 dr), although the ee of the isomers are nearly perfect (96% and 99% ee, respectively; see Scheme 12).<sup>48</sup> In contrast, the  $[\text{Ir}(\text{cod})\text{Cl}]_2 \cdot N$ -arylphosphoramidite (**L3**) complex<sup>49</sup> was found to furnish the desired product in 98% ee, >20:1 dr and excellent branched to linear ratio.

The reaction proceeds with high yield and selectivity using a wide range of substrates variable on the enolate portion as well as the electrophile (Table 6). With further exploration, we found that a modified protocol is amenable to acyclic  $\beta$ -ketoesters as well, again with tolerance to a wide array of substituent groups and functionality (Table 7).<sup>50</sup>

Combining our fluoride-triggered decarboxylative allylic alkylation<sup>51</sup> and the iridium chemistry together, we have developed a sequential double allylic alkylation procedure to selectively program the diastereomer that is furnished within the stereochemical dyad. We found that 2-(trimethylsilyl)ethyl  $\beta$ -ketoester substrates successfully engage in iridium-catalyzed allylic alkylation to generate the desired product with excellent regio- and enantioselectivity. Subsequently, treatment of the product (**44**) with allyl methyl carbonate and catalyst derived from  $\text{Pd}_2(\text{dba})_3$  and PHOX ligand (**L4**), in the presence of tetrabutylammonium difluorotriphenylsilicate (TBAT), generated the desired dialkylated  $\alpha$ -quaternary ketone **45B** in good yield and diastereoselectivity (Table 8, entry 1). Through choice of ligand, we can alter the selectivity to favor the ketone **45A** in high dr (12:1–18:1) and yield (80–87%) with several 2-substituted allyl carbonates (entries 2–4).

## 6. Conclusions

The development of a suite of catalytic asymmetric transformations by our group for the preparation of quaternary stereocenters provides access to a broad range of enantioenriched, high-value, small molecule building blocks (Figure 3). We have developed methods that readily produce 3,3-disubstituted oxindoles,  $\beta$ -quaternary ketones,  $\alpha$ -quaternary ketones,



and  $\alpha$ -quaternary lactams. These building blocks can be further derivatized to a much larger collection of compounds bearing quaternary stereogenicity. We anticipate that the synthetic methods developed by our group and the advancements that synthetic chemists are making as a whole toward the synthesis of challenging stereochemically rich molecules will find increasing future application in drug discovery and design. These methods move us into previously unexplored chemical space that may be brought to bear on problems of a medicinal nature, with potential enhancements in biochemical, pharmacological, and physiological properties.

## ACKNOWLEDGMENT

The authors are indebted to the efforts of many members of the Stoltz Research Group whose dedicated efforts produced the chemistry described within this account. For financial support, we thank NIH-NIGMS (R01GM080269), Amgen, the Gordon and Betty Moore Foundation, Caltech, and the Resnick Sustainability Institute at Caltech (graduate fellowship to Y.L.). S.-J.H. thanks Fulbright (Foreign Student Program, No. 15111120) and the Ilju Foundation of Education & Culture (Predoctoral Research Fellowship) for financial support. Shanghai Institute of Organic Chemistry (SIOC) is thanked for a postdoctoral fellowship to W.-B. L.

## Biographies

**Yiyang Liu** received his B.S. degree in Chemistry from Peking University in 2010 under the direction of Prof. Jianbo Wang and Prof. Yan Zhang. He then moved to the California Institute of Technology and began his doctoral studies under the guidance of Professor Brian M. Stoltz. His graduate research focuses on chemical synthesis using renewable resources.

**Seo-Jung Han** graduated with a B.S. in chemistry from Sogang University in 2008. She received her M.S. degree in 2010 from Sogang University under the direction of Professor Duck-Hyung Lee. She then moved to Caltech and began her doctoral studies under the guidance of Professor Brian M. Stoltz. Her graduate research focuses on total synthesis of complex polycyclic natural products.

**Wen-Bo Liu** was born in China and he received his Bachelor's Degree in Chemistry from the Nankai University in 2006. He obtained his Ph.D. in organic chemistry (2011) from the Shanghai Institute of Organic Chemistry (SIOC) under the supervision of Professor Li-Xin Dai and Professor Shu-Li You. Then he joined the laboratory of Professor Brian M. Stoltz at Caltech as a postdoctoral scholar, working on asymmetric catalysis and sustainable chemistry.

**Brian M. Stoltz** was born in Philadelphia, PA in 1970 and obtained his B.S. degree from the Indiana University of Pennsylvania in Indiana, PA. After graduate work at Yale University in the labs of John L. Wood and an NIH postdoctoral fellowship at Harvard with E. J. Corey he took a position at the California Institute of Technology. A member of the Caltech faculty since 2000, he is currently Professor of Chemistry. His research interests lie in the development of new methodology for general applications in synthetic chemistry.

## REFERENCES

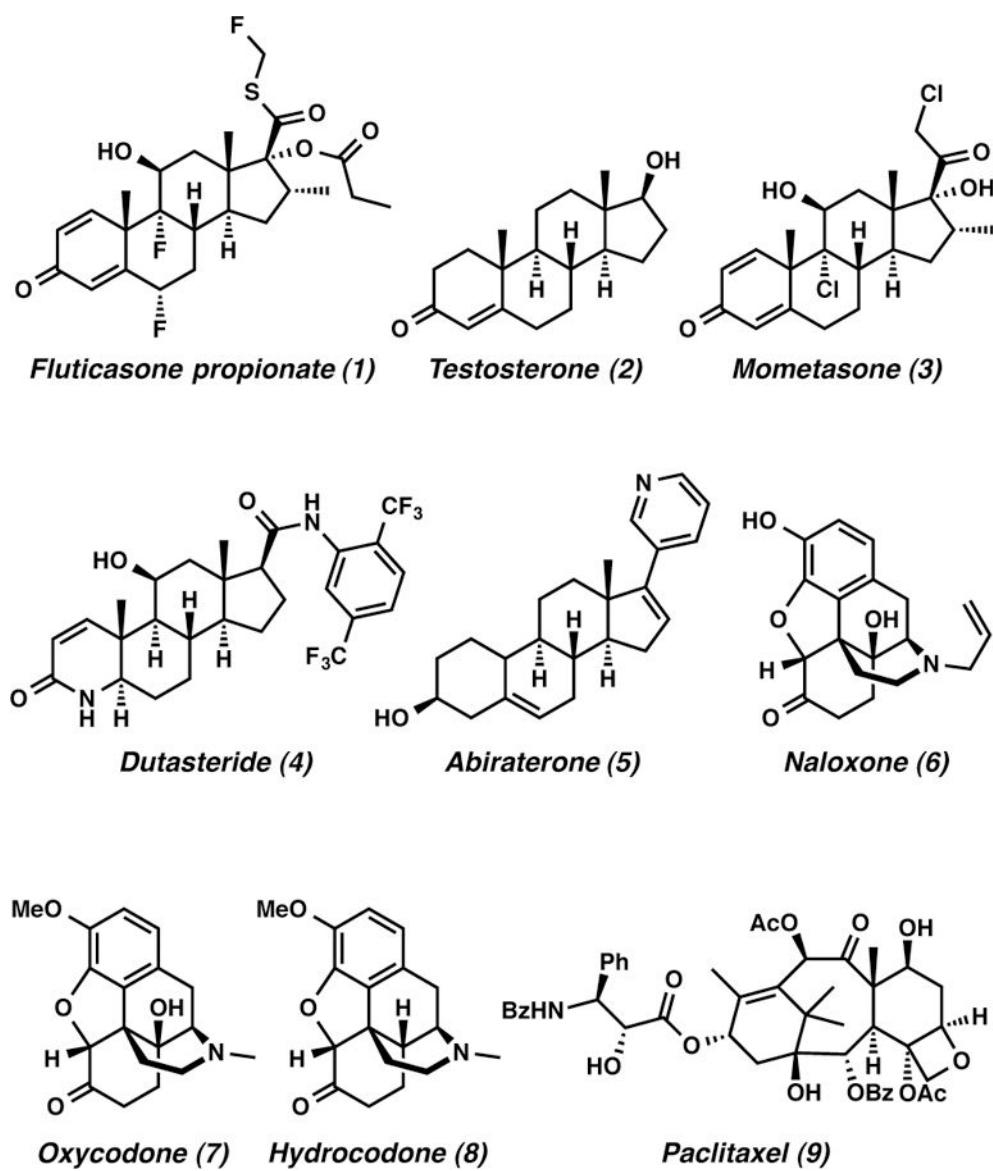
- (1). Richie TJ; MacDonald SJF. The impact of aromatic ring count on compound developability – are too many aromatic rings a liability in drug design? *Drug Discov. Today* 2009, 14, 1011–1020.

- (2). Lovering F; Bikker J; Humblet C Escape from Flatland: Increasing Saturation as an Approach to Improving Clinical Success. *J. Med. Chem* 2009, 52, 6752–6756. [PubMed: 19827778]
- (3). (a) Trost BM; Jiang C Catalytic Enantioselective Construction of All-Carbon Quaternary Stereocenters. *Synthesis* 2006, 369–396. (b) Corey EJ; Guzman-Perez A The Catalytic Enantioselective Construction of Molecules with Quaternary Carbon Stereocenters. *Angew. Chem., Int. Ed* 1998, 37, 388–401.
- (4). [http://cbc.arizona.edu/njardarson/group/sites/default/files/Top200%20Pharmaceutical%20Products%20by%20US%20Retail%20Sales%20in%202012\\_0.pdf](http://cbc.arizona.edu/njardarson/group/sites/default/files/Top200%20Pharmaceutical%20Products%20by%20US%20Retail%20Sales%20in%202012_0.pdf)
- (5). Castro AMM Claisen Rearrangement over the Past Nine Decades. *Chem. Rev* 2004, 104, 2939–3002. [PubMed: 15186185]
- (6). Corey EJ Catalytic Enantioselective Diels–Alder Reactions: Methods, Mechanistic Fundamentals, Pathways, and Applications. *Angew. Chem., Int. Ed* 2002, 41, 1650–1667.
- (7). (a) Galliford CV; Scheidt KA Pyrrolidiny-Spirooxindole Natural Products as Inspirations for the Development of Potential Therapeutic Agents. *Angew. Chem., Int. Ed* 2007, 46, 8748–8758. (b) Marti C; Carreira EM Total Synthesis of (–)-Spirotryprostatin B: Synthesis and Related Studies. *J. Am. Chem. Soc* 2005, 127, 11505–11515. [PubMed: 16089481] (c) Edmondson S; Danishefsky SJ; Sepp-Lorenzino L; Rosen N Total Synthesis of Spirotryprostatin A, Leading to the Discovery of Some Biologically Promising Analogues. *J. Am. Chem. Soc* 1999, 121, 2147–2155.
- (8). Ding K; Lu Y; Nikolovska-Coleska Z; Wang G; Qiu S; Shangary S; Gao W; Qin D; Stuckey J; Krajewski K; Roller PP; Wang S Structure-Based Design of Spiro-oxindoles as Potent, Specific Small-Molecule Inhibitors of the MDM2–p53 Interaction. *J. Med. Chem* 2006, 49, 3432–3435. [PubMed: 16759082]
- (9). Reviews: (a) Zhou F; Liu Y-L; Zhou J Catalytic Asymmetric Synthesis of Oxindoles Bearing a Tetrasubstituted Stereocenter at the C-3 Position. *Adv. Synth. Catal* 2010, 352, 1381–1407. (b) Klein JEMN; Taylor RJK Transition-Metal-Mediated Routes to 3,3-Disubstituted Oxindoles through Anilide Cyclisation. *Eur. J. Org. Chem* 2011, 6821–6841. (c) Dalpozzo R; Bartoli G; Bencivenni G Recent Advances in Organocatalytic Methods for the Synthesis of Disubstituted 2- and 3-Indolinones. *Chem. Soc. Rev* 2012, 41, 7247–7290. [PubMed: 22899437] (d) Singh GS; Desta ZY Isatins As Privileged Molecules in Design and Synthesis of Spiro-Fused Cyclic Frameworks. *Chem. Rev* 2012, 112, 6104–6155. [PubMed: 22950860]
- (10). Recent examples: (a) Hu F-L; Wei Y; Shi M Phosphine-Catalyzed Asymmetric [4+1] Annulation of Activated  $\alpha,\beta$ -Unsaturated Ketones with Morita–Baylis–Hillman Carbonates: Enantioselective Synthesis of Spirooxindoles Containing Two Adjacent Quaternary Stereocenters. *Chem. Commun* 2014, 50, 8912–8914. (b) Cao Z-Y; Wang Y-H; Zeng X-P; Zhou J Catalytic Asymmetric Synthesis of 3,3-Disubstituted Oxindoles: Diazoindole Joins the Field. *Tetrahedron Lett* 2014, 55, 2571–2584. (c) Trost BM; Osipov M Palladium-Catalyzed Asymmetric Construction of Vicinal All-Carbon Quaternary Stereocenters and its Application to the Synthesis of Cyclotryptamine Alkaloids. *Angew. Chem., Int. Ed* 2013, 52, 9176–9181.
- (11). Krishnan S; Stoltz BM Preparation of 3,3-Disubstituted Oxindoles by Addition of Malonates to 3-Halo-3-oxindoles. *Tetrahedron Lett* 2007, 48, 7571–7573.
- (12). Han S-J; Vogt F; Krishnan S; May JA; Gatti M; Virgil SC; Stoltz BM Diastereodivergent Synthetic Strategy for the Syntheses of Communesin F and Perophoramidine. *Org. Lett* 2014, 16, 3316–3319. [PubMed: 24909760]
- (13). Ma S; Han X; Krishnan S; Virgil SC; Stoltz BM Catalytic Enantioselective Stereoblative Alkylation of 3-Halo-oxindoles: Facile Access to Oxindoles with C3 All-Carbon Quaternary Stereocenters. *Angew. Chem., Int. Ed* 2009, 48, 8037–8041.
- (14). Hawner C; Alexakis A Metal-Catalyzed Asymmetric Conjugate Addition Reaction: Formation of Quaternary Stereocenters. *Chem. Commun* 2010, 46, 7295–7306.
- (15). Hird AW; Hoveyda AH Catalytic Enantioselective Alkylations of Tetrasubstituted Olefins. Synthesis of All-Carbon Quaternary Stereogenic Centers through Cu-Catalyzed Asymmetric Conjugate Additions of Alkylzinc Reagents to Enones. *J. Am. Chem. Soc* 2005, 127, 14988–14989. [PubMed: 16248613]

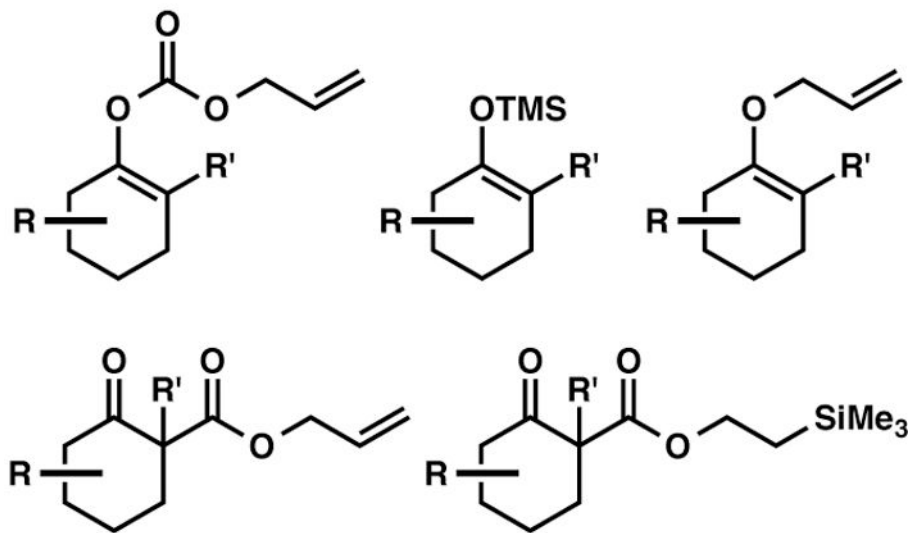
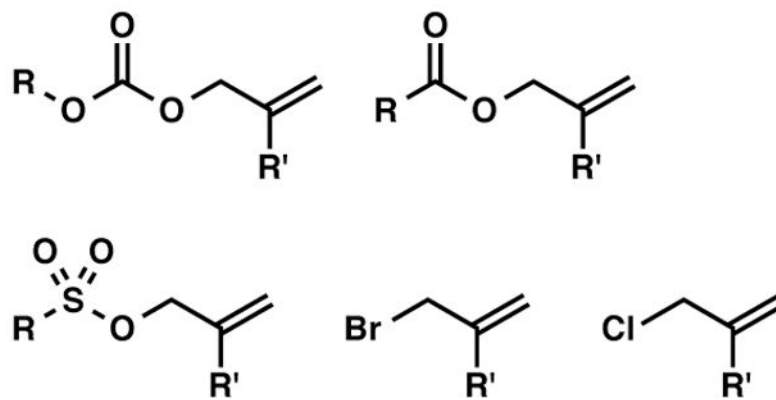
- (16). d'Augustin M; Palais L; Alexakis A Enantioselective Copper-Catalyzed Conjugate Addition to Trisubstituted Cyclohexenones: Construction of Stereogenic Quaternary Centers. *Angew. Chem., Int. Ed* 2005, 44, 1376–1378.
- (17). Martin D; Kehrl S; d'Augustin M; Clavier H; Mauduit M; Alexakis A Copper-Catalyzed Asymmetric Conjugate Addition of Grignard Reagents to Trisubstituted Enones. Construction of All-Carbon Quaternary Chiral Centers. *J. Am. Chem. Soc* 2006, 128, 8416–8417. [PubMed: 16802804]
- (18). Takaya Y; Ogasawara M; Hayashi T Rhodium-Catalyzed Asymmetric 1,4-Addition of Aryl- and Alkenylboronic Acids to Enones. *J. Am. Chem. Soc* 1998, 120, 5579–5580.
- (19). Shintani R; Duan W-L; Hayashi T Rhodium-Catalyzed Asymmetric Construction of Quaternary Carbon Stereocenters: Ligand- Dependent Regiocontrol in the 1,4-Addition to Substituted Maleimides. *J. Am. Chem. Soc* 2006, 128, 5628–5629. [PubMed: 16637617]
- (20). Shintani R; Tsutsumi Y; Nagaosa M; Nishimura T; Hayashi T Sodium Tetraarylbates as Effective Nucleophiles in Rhodium/Diene-Catalyzed 1,4-Addition to  $\beta,\beta$ -Disubstituted  $\alpha,\beta$ -Unsaturated Ketones: Catalytic Asymmetric Construction of Quaternary Carbon Stereocenters. *J. Am. Chem. Soc* 2009, 131, 13588–13589. [PubMed: 19728707]
- (21). Gutnov A Palladium-Catalyzed Asymmetric Conjugate Addition of Aryl–Metal Species. *Eur. J. Org. Chem* 2008, 4547–4554.
- (22). Lin S; Lu X Cationic Pd(II)/Bipyridine-Catalyzed Conjugate Addition of Arylboronic Acids to  $\beta,\beta$ -Disubstituted Enones: Construction of Quaternary Carbon Centers. *Org. Lett* 2010, 12, 2536–2539. [PubMed: 20450192]
- (23). Kikushima K; Holder JC; Gatti M; Stoltz BM Palladium-Catalyzed Asymmetric Conjugate Addition of Arylboronic Acids to Five-, Six-, and Seven-Membered  $\beta$ -Substituted Cyclic Enones: Enantioselective Construction of All-Carbon Quaternary Stereocenters. *J. Am. Chem. Soc* 2011, 133, 6902–6905. [PubMed: 21495647]
- (24). Holder JC; Zou L; Marziale AN; Liu P; Lan Y; Gatti M; Kikushima K; Houk KN; Stoltz BM Mechanism and Enantioselectivity in Palladium-Catalyzed Conjugate Addition of Arylboronic Acids to  $\beta$ -Substituted Cyclic Enones: Insights from Computation and Experiment. *J. Am. Chem. Soc* 2013, 135, 14996–15007. [PubMed: 24028424]
- (25). Behenna DC; Stoltz BM Natural Products as Inspiration for Reaction Development: Catalytic Enantioselective Decarboxylative Reactions of Prochiral Enolate Equivalents. *Top. Organomet. Chem* 2013, 44, 281–314.
- (26). Trost BM; Van Vranken DL Asymmetric Transition Metal-Catalyzed Allylic Alkylations. *Chem. Rev* 1996, 96, 395–422. [PubMed: 11848758]
- (27). Trost BM Asymmetric Allylic Alkylation, an Enabling Methodology. *J. Org. Chem* 2004, 69, 5813–5837. [PubMed: 15373468]
- (28). Helmchen G Enantioselective Palladium-Catalyzed Allylic Substitutions with Asymmetric Chiral Ligands. *J. Organomet. Chem* 1999, 576, 203–214.
- (29). Luchaco-Cullis CA; Mizutani H; Murphy KE; Hoveyda AH Modular Pyridinyl Peptide Ligands in Asymmetric Catalysis: Enantioselective Synthesis of Quaternary Carbon Atoms Through Copper-Catalyzed Allylic Substitutions. *Angew. Chem., Int. Ed* 2001, 40, 1456–1460.
- (30). Trost BM; Schroeder GM Palladium-Catalyzed Asymmetric Alkylation of Ketone Enolates. *J. Am. Chem. Soc* 1999, 121, 6759–6760.
- (31). (a) Hayashi T; Kanehira K; Hagihara T; Kumada M Asymmetric Synthesis Catalyzed by Chiral Ferrocenylphosphine-Transition Metal Complexes. 5. Palladium-Catalyzed Asymmetric Allylation of Active Methine Compounds. *J. Org. Chem* 1988, 53, 113–120. (b) Sawamura M; Nagata H; Sakamoto H; Ito Y Chiral Phosphine Ligands Modified by Crown Ethers: an Application to Palladium-Catalyzed Asymmetric Allylation of  $\beta$ -Diketones. *J. Am. Chem. Soc* 1992, 114, 2586–2592. (c) Trost BM; Radinov R; Grenzer EM Asymmetric Alkylation of  $\beta$ -Ketoesters. *J. Am. Chem. Soc* 1997, 119, 7879–7880.
- (32). (a) Shimizu I; Yamada T; Tsuji J Palladium-Catalyzed Rearrangement of Allylic Esters of Acetoacetic Acid to Give  $\gamma,\delta$ -Unsaturated Methyl Ketones. *Tetrahedron Lett* 1980, 21, 3199–3202. (b) Tsuji J; Minami I; Shimizu I Palladium-Catalyzed Allylation of Ketones and Aldehydes via Allyl Enol Carbonates. *Tetrahedron Lett* 1983, 24, 1793–1796.

- (33). Behenna DC; Stoltz BM The Enantioselective Tsuji Allylation. *J. Am. Chem. Soc* 2004, 126, 15044–15045. [PubMed: 15547998]
- (34). Mohr JT; Behenna DC; Harned AM; Stoltz BM Deracemization of Quaternary Stereocenters by Pd-Catalyzed Enantioconvergent Decarboxylative Allylation of Racemic  $\beta$ -Ketoesters. *Angew. Chem., Int. Ed* 2005, 44, 6924–6927.
- (35). Seto M; Roizen JL; Stoltz BM Catalytic Enantioselective Alkylation of Substituted Dioxanone Enol Ethers: Ready Access to C( $\alpha$ )-Tetrasubstituted Hydroxyketones, Acids, and Esters. *Angew. Chem., Int. Ed* 2008, 47, 6873–6876.
- (36). Reeves CM; Eidamshaus C; Kim J; Stoltz BM Enantioselective Construction of  $\alpha$ -Quaternary Cyclobutanones by Catalytic Asymmetric Allylic Alkylation. *Angew. Chem., Int. Ed* 2013, 52, 6718–6721.
- (37). Behenna DC; Liu Y; Yurino T; Kim J; White DE; Virgil SC; Stoltz BM Enantioselective Construction of Quaternary N- Heterocycles by Palladium-Catalysed Decarboxylative Allylic Alkylation of Lactams. *Nature Chem* 2012, 4, 130–133.
- (38). Korch KM; Eidamshaus C; Behenna DC; Nam S; Home D; Stoltz BM Enantioselective Synthesis of  $\alpha$ -Secondary and  $\alpha$ -Tertiary Piperazin-2-ones and Piperazines by Catalytic Asymmetric Allylic Alkylation. *Angew. Chem., Int. Ed* DOI: 10.1002/anie.201408609.
- (39). Trost BM; Xu J Regio- and Enantioselective Pd-Catalyzed Allylic Alkylation of Ketones through Allyl Enol Carbonates. *J. Am. Chem. Soc* 2005, 127, 2846–2847. [PubMed: 15740108]
- (40). (a) Nakamura M; Hajra A; Endo K; Nakamura E Synthesis of Chiral  $\alpha$ -Fluoroketones through Catalytic Enantioselective Decarboxylation. *Angew. Chem., Int. Ed* 2005, 44, 7248–7251. (b) Bélanger É; Cantin K; Messe O; Tremblay M; Paquin J-F Enantioselective Pd-Catalyzed Allylation Reaction of Fluorinated Silyl Enol Ethers. *J. Am. Chem. Soc* 2007, 129, 1034–1035. [PubMed: 17263376]
- (41). Grenning AJ; Van Allen CK; Maji T; Lang SB; Tunge JA Development of Asymmetric Deacylative Allylation. *J. Org. Chem* 2013, 78, 7281–7287. [PubMed: 23734611]
- (42). Schulz SR; Blechert S Palladium-Catalyzed Synthesis of Substituted Cycloheptane-1,4-diones by an Asymmetric Ring-Expanding Allylation (AREA). *Angew. Chem., Int. Ed* 2007, 46, 3966–3970.
- (43). Nahra F; Macé Y; Lambin D; Riant O Copper/Palladium-Catalyzed 1,4 Reduction and Asymmetric Allylic Alkylation of  $\alpha,\beta$ -Unsaturated Ketones: Enantioselective Dual Catalysis. *Angew. Chem., Int. Ed* 2013, 52, 3208–3212.
- (44). Streuff J; White DE; Virgil SC; Stoltz BM A Palladium-Catalysed Enolate Alkylation Cascade for the Formation of Adjacent Quaternary and Tertiary Stereocentres. *Nature Chem* 2010, 2, 192–196. [PubMed: 20697457]
- (45). Liu W-B; Reeves CM; Virgil SC; Stoltz BM Construction of Vicinal Tertiary and All-Carbon Quaternary Stereocenters via Ir-Catalyzed Regio-, Diastereo-, and Enantioselective Allylic Alkylation and Applications in Sequential Pd Catalysis. *J. Am. Chem. Soc* 2013, 135, 10626–10629. [PubMed: 23829704]
- (46). For the first examples: (a) Takeuchi R; Kashio M Highly Selective Allylic Alkylation with a Carbon Nucleophile at the More Substituted Allylic Terminus Catalyzed by an Iridium Complex: An Efficient Method for Constructing Quaternary Carbon Centers. *Angew. Chem., Int. Ed. Engl* 1997, 36, 263–265. (b) Janssen JP; Helmchen G First Enantioselective Alkylations of Monosubstituted Allylic Acetates Catalyzed by Chiral Iridium Complexes. *Tetrahedron Lett* 1997, 38, 8025–8026. (c) For reviews: Helmchen G; Dahnz A; Dübon P; Schelwies M; Weihofen R Iridium-Catalysed Asymmetric Allylic Substitutions. *Chem. Commun* 2007, 675–691. (d) Hartwig JF; Pouy MJ Iridium-Catalyzed Allylic Substitution. *Top. Organomet. Chem* 2011, 34, 169–208. (e) Tosatti P; Nelson A; Marsden SP Recent Advances and Applications of Iridium-Catalysed Asymmetric Allylic Substitution. *Org. Biomol. Chem* 2012, 10, 3147–3163. [PubMed: 22407450]
- (47). Teichert JF; Feringa BL Phosphoramidites: Privileged Ligands in Asymmetric Catalysis. *Angew. Chem. Int. Ed* 2010, 49, 2486–2528.
- (48). (a) Wu Q-F; He H; Liu W-B; You S-L Enantioselective Construction of Spiroindolenines by Ir-Catalyzed Allylic Alkylation Reactions. *J. Am. Chem. Soc* 2010, 132, 11418–11419. [PubMed: 20677752] (b) Kanayama T; Yoshida K; Miyabe H; Takemoto Y Enantio- and Diastereoselective

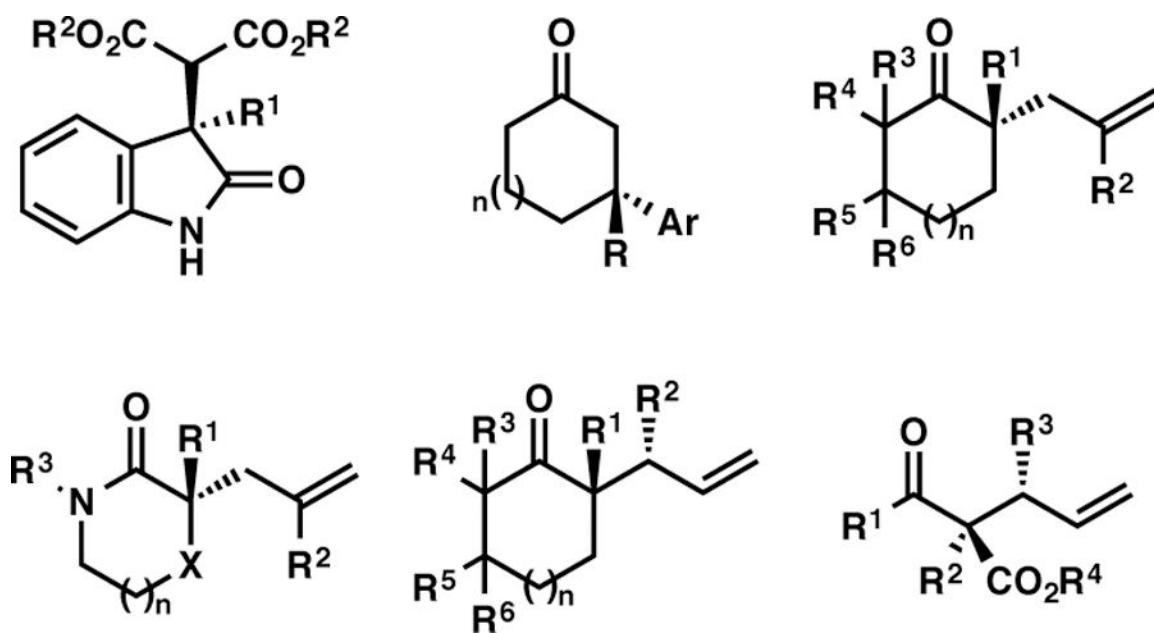
- Ir-Catalyzed Allylic Substitutions for Asymmetric Synthesis of Amino Acid Derivatives. *Angew. Chem., Int. Ed* 2003, 42, 2054–2056. (c)Chen W; Hartwig JF Control of Diastereoselectivity for Iridium-Catalyzed Allylation of a Prochiral Nucleophile with a Phosphate Counterion. *J. Am. Chem. Soc* 2013, 135, 2068–2071. [PubMed: 23286279] (d)Krautwald S; Sarlah D; Schafroth MA; Carreira EM Enantio- and Diastereodivergent Dual Catalysis:  $\alpha$ -Allylation of Branched Aldehydes. *Science* 2013, 340, 1065–1068. [PubMed: 23723229]
- (49). Liu W-B; Zheng C; Zhuo C-X; Dai L-X; You S-L Iridium-Catalyzed Allylic Alkylation Reaction with N-Aryl Phosphoramidite Ligands: Scope and Mechanistic Studies. *J. Am. Chem. Soc* 2012, 134, 4812–4821. [PubMed: 22309279]
- (50). Liu W-B; Reeves CM; Stoltz BM Enantio-, Diastereo-, and Regioselective Iridium-Catalyzed Asymmetric Allylic Alkylation of Acyclic  $\beta$ -Ketoesters. *J. Am. Chem. Soc* 2013, 135, 17298–17301. [PubMed: 24160327]
- (51). Reeves CM; Behenna DC; Stoltz BM Development of (Trimethylsilyl)ethyl Ester Protected Enolates and Applications in Palladium-Catalyzed Enantioselective Allylic Alkylation: Intermolecular Cross-Coupling of Functionalized Electrophiles. *Org. Lett* 2014, 16, 2314–2317. [PubMed: 24724872]



**Figure 1.**  
Drug molecules containing quaternary stereocenters.

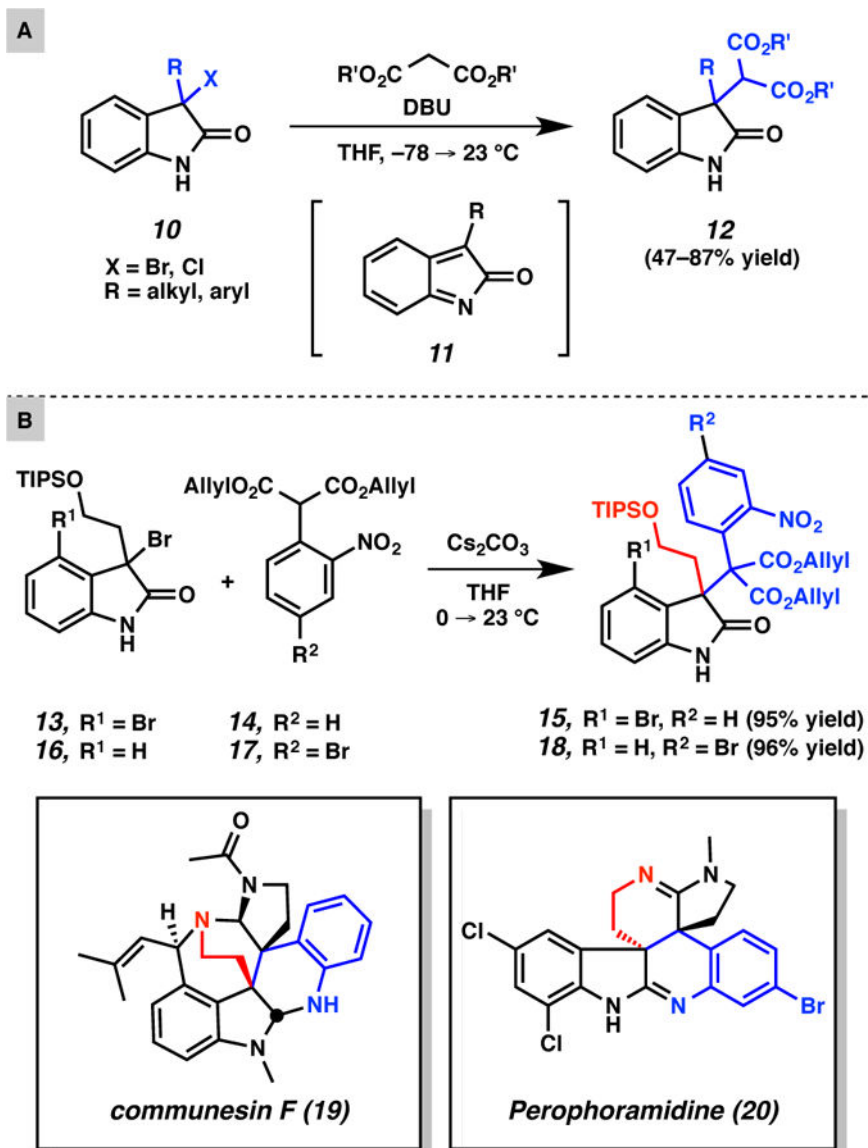
**Masked enolate synthons:****Allylic Electrophiles:**

**Figure 2.**  
Substrate possibilities for the enantioselective alkylation reaction.

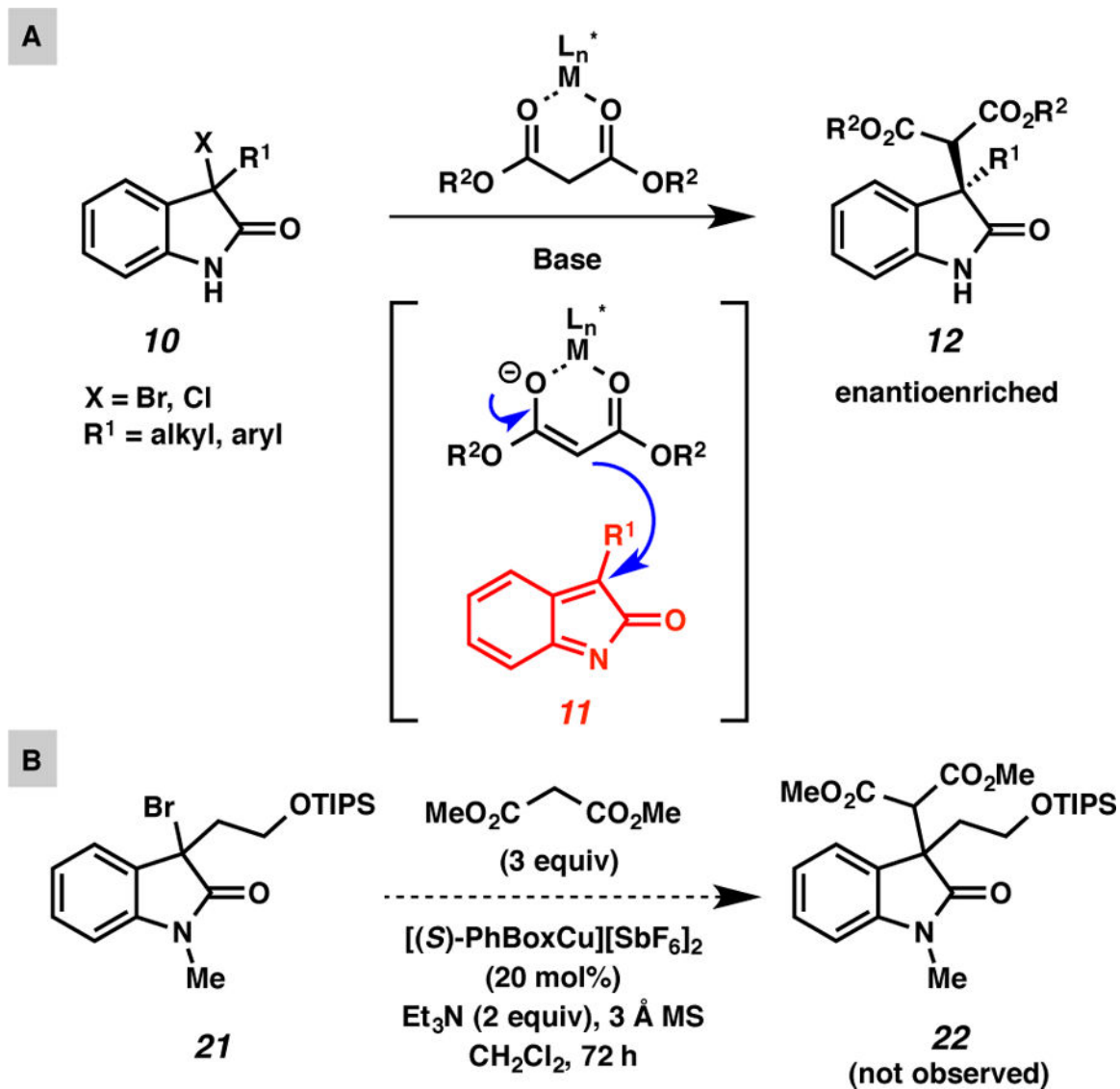


**Figure 3.**  
Enantioenriched building blocks accessible by our synthetic methods.

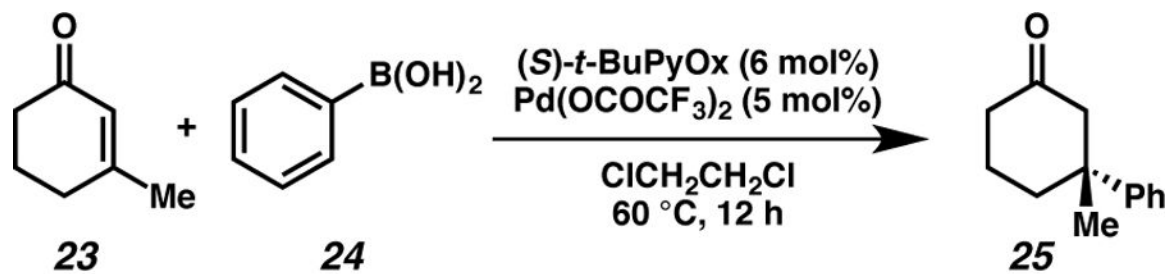




**Scheme 1.**  
Alkylations of 3-haloindoles.



Scheme 2.  
Alkylations of 3-haloindoles via reactive prochiral indolone 11.



**A. No added H<sub>2</sub>O**

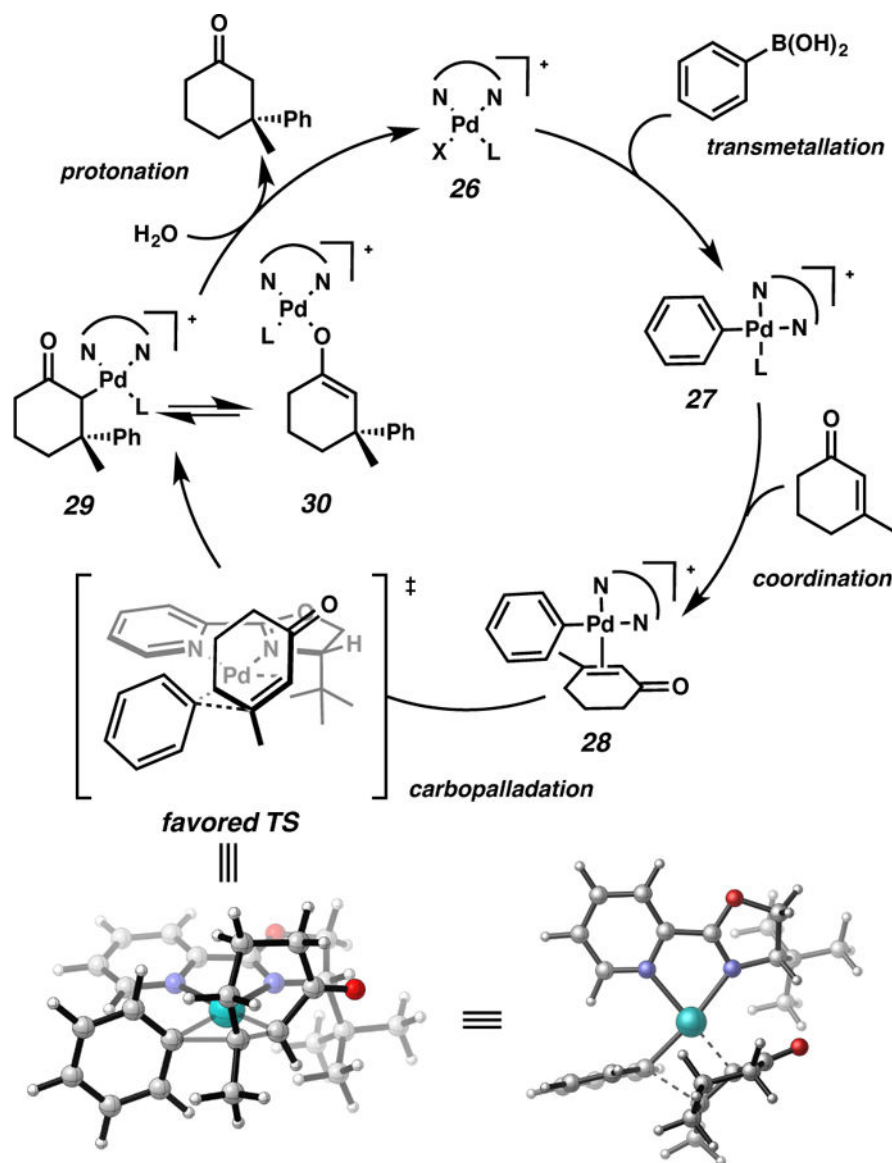
**B. 5 equiv H<sub>2</sub>O**

**Incomplete conversion (9 mmol scale)**

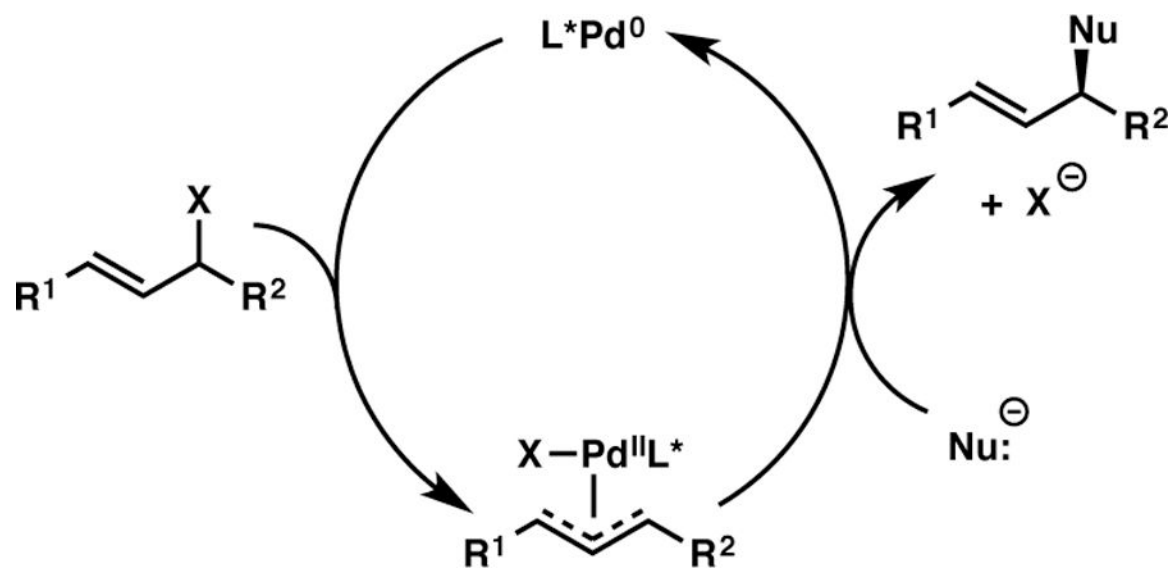
**97% yield, 91% ee (22 mmol scale)**

**Scheme 3.**

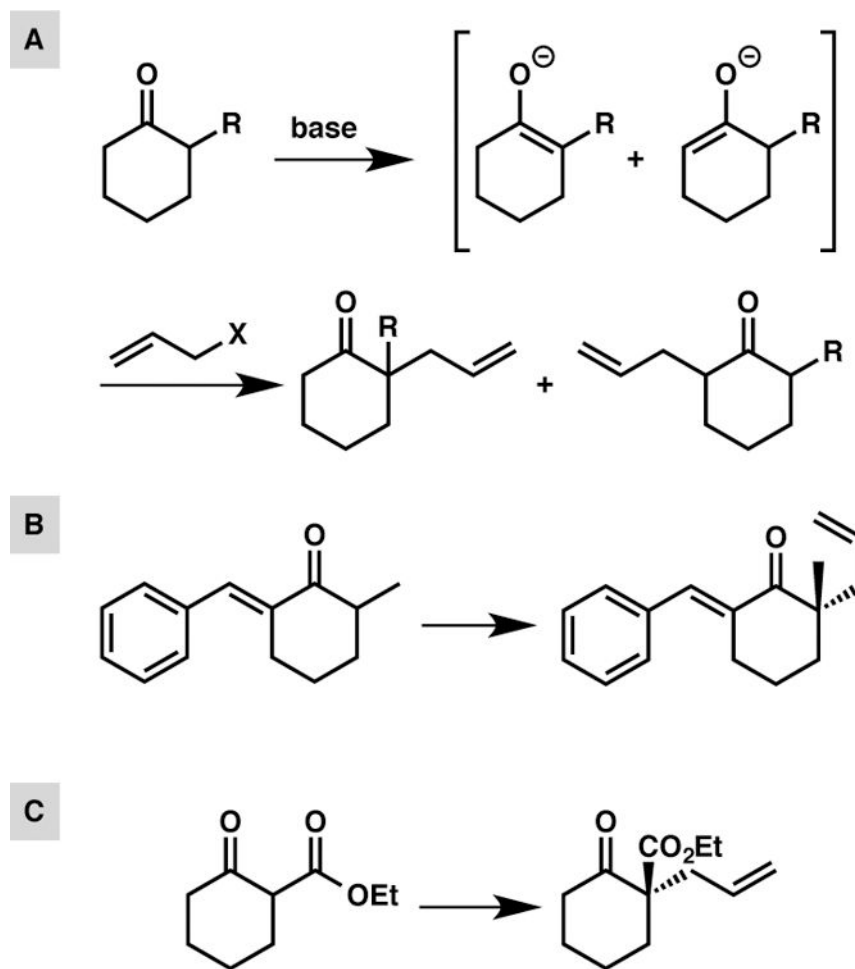
Large scale conjugate additions.



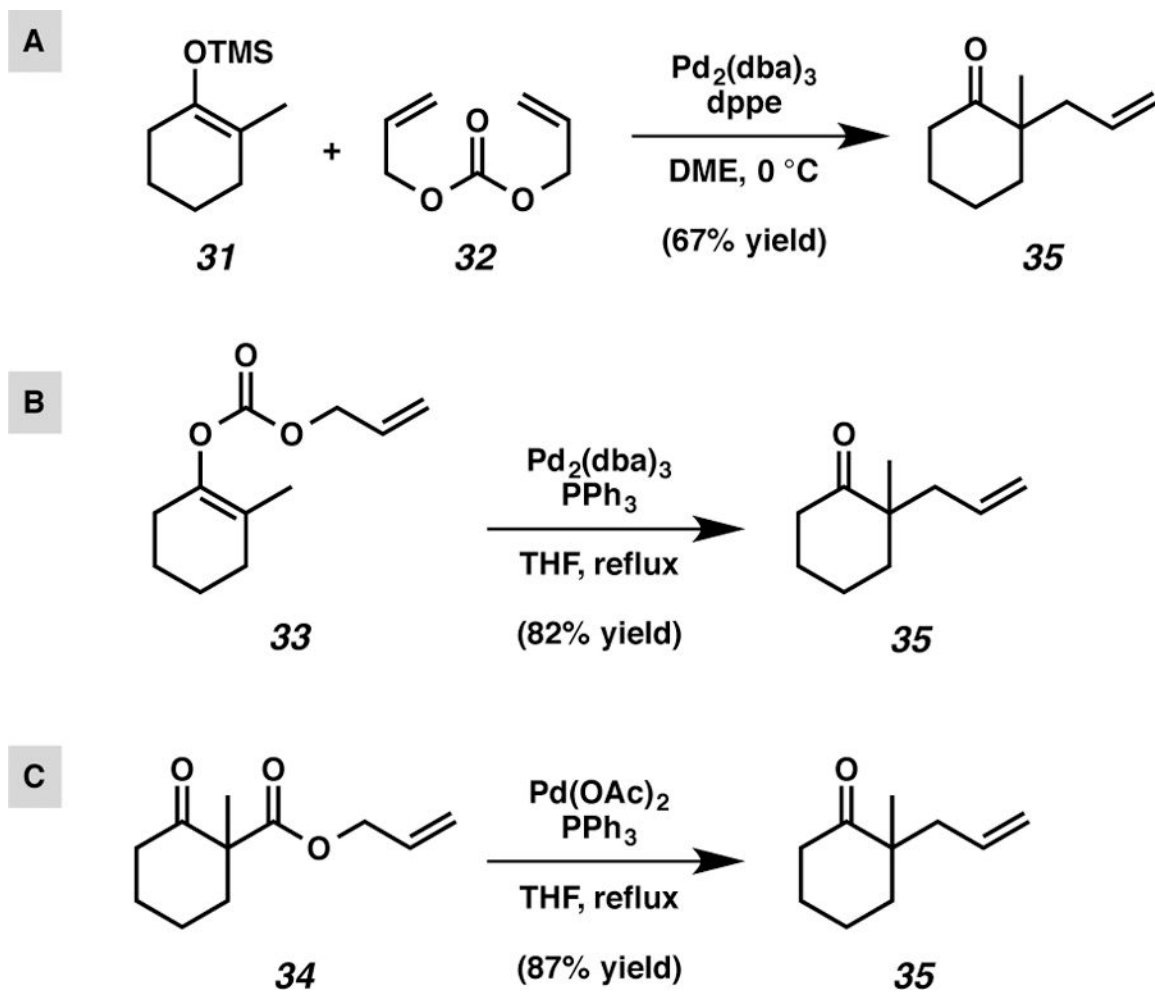
**Scheme 4.**  
Mechanistic rationale for the asymmetric conjugate addition.



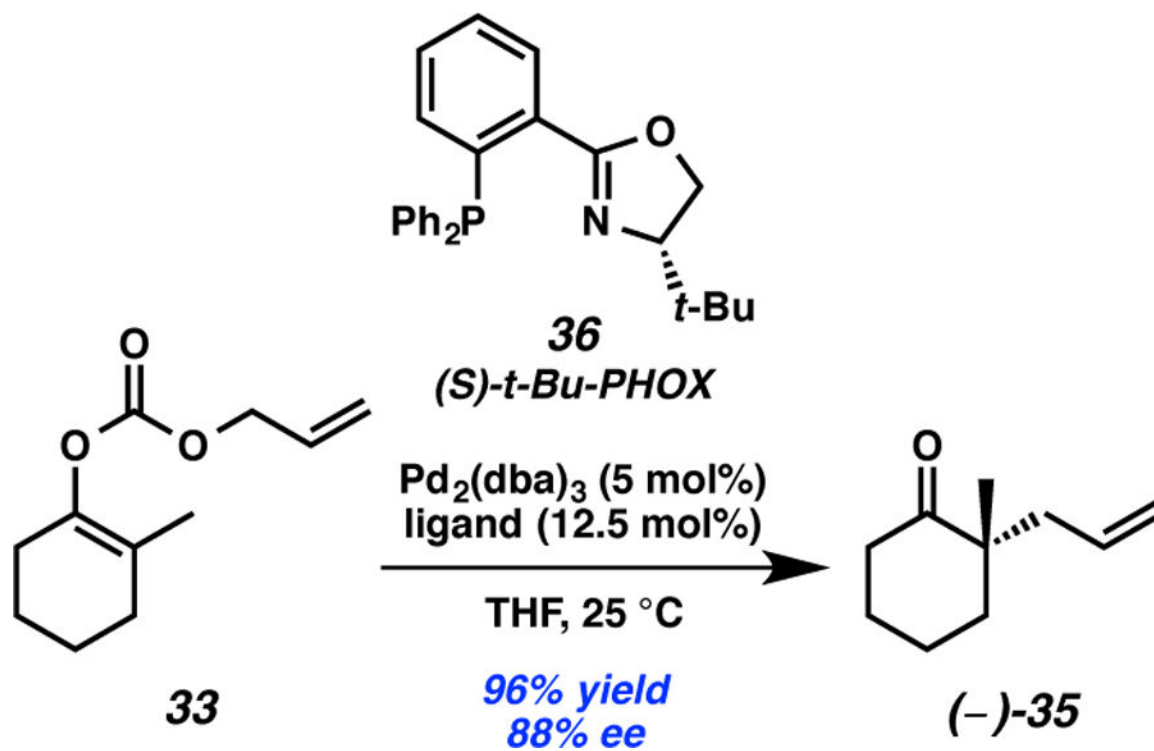
**Scheme 5.**  
General mechanism of Pd-catalyzed Asymmetric Allylic Alkylation.



**Scheme 6.**  
Challenges in alkylation of nonsymmetrical ketones.

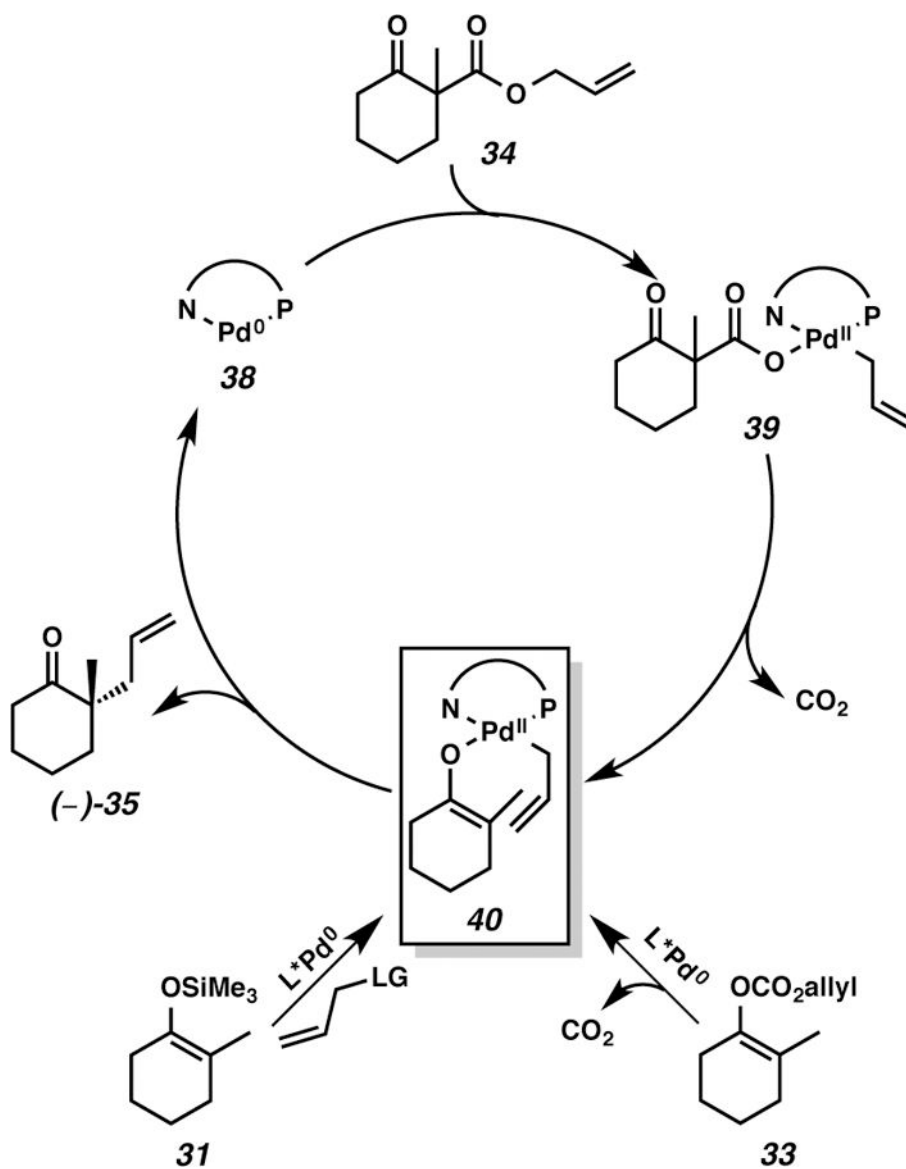


**Scheme 7.**  
The Tsuji allylic alkylation.

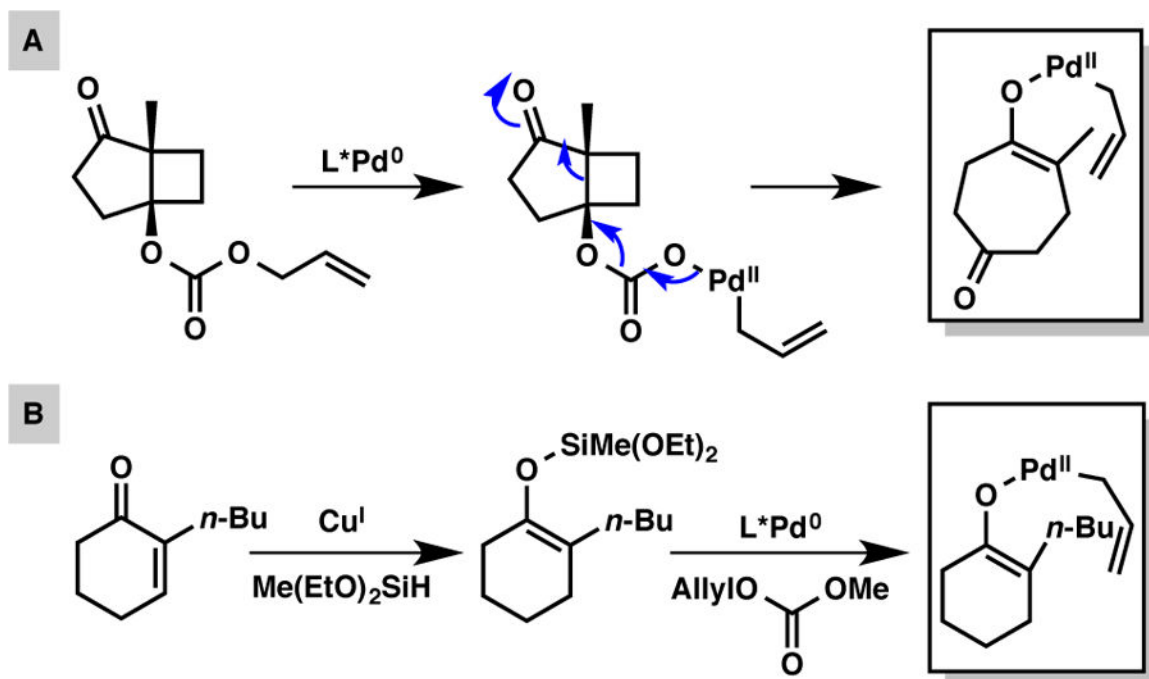
**Scheme 8.**

Discovery of an enantioselective catalyst system for the asymmetric Tsuji allylic alkylation.

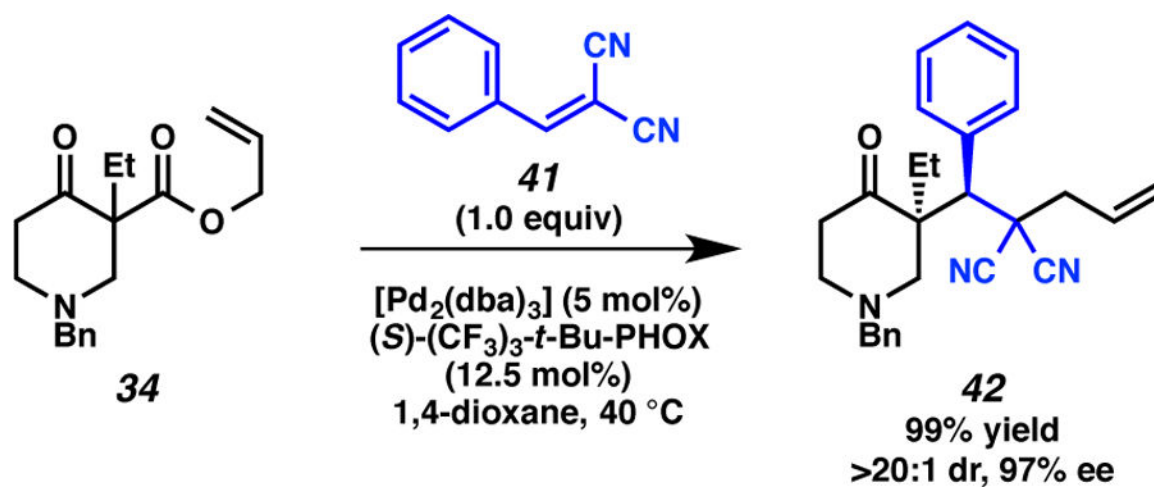




**Scheme 9.**  
Proposed mechanism for palladium-catalyzed allylic alkylation.

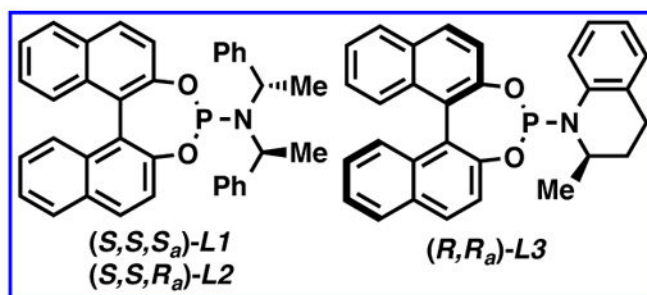
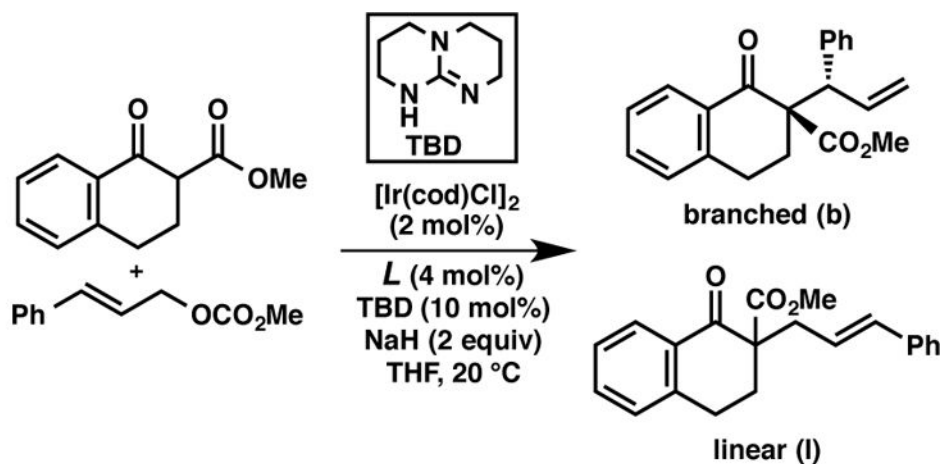


**Scheme 10.**  
Generation of palladium enolate intermediates from other starting materials.



**Scheme 11.**

Asymmetric enolate alkylation cas-cade with different electrophiles.



ligand	b:l	for branched	
		dr	ee (%) <sup>a</sup>
<b>L1</b>	>95:5	1:1	96 (99) <sup>a</sup>
<b>L2</b>	>95:5	1:2	32 (3) <sup>a</sup>
<b>L3</b>	<b>95:5</b>	<b>&gt;20:1</b>	<b>98</b>

<sup>a</sup> (ee) for alternate diastereomer.

**Scheme 12.**

Ir-catalyzed allylic alkylation of cyclic  $\alpha$ -substituted  $\beta$ -ketoesters. <sup>a</sup> (ee) for alternate diastereomer.

Table 1.

Enantioselective alkylation of 3-haloindoles.

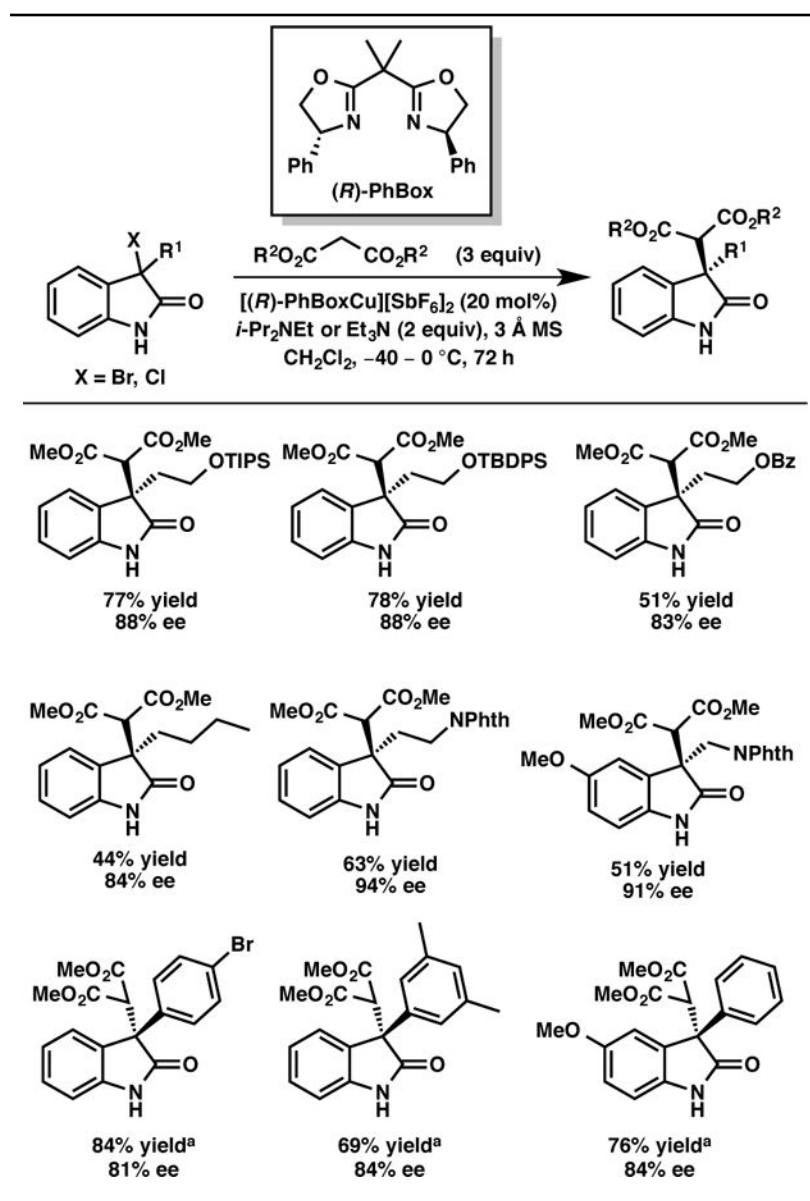
<sup>a</sup> Used 3-aryl-3-chloroindoles as substrates and (*S*)-PhBox as ligand.

Table 2.

Asymmetric addition of arylboronic acids to 3-substituted cyclic enones.

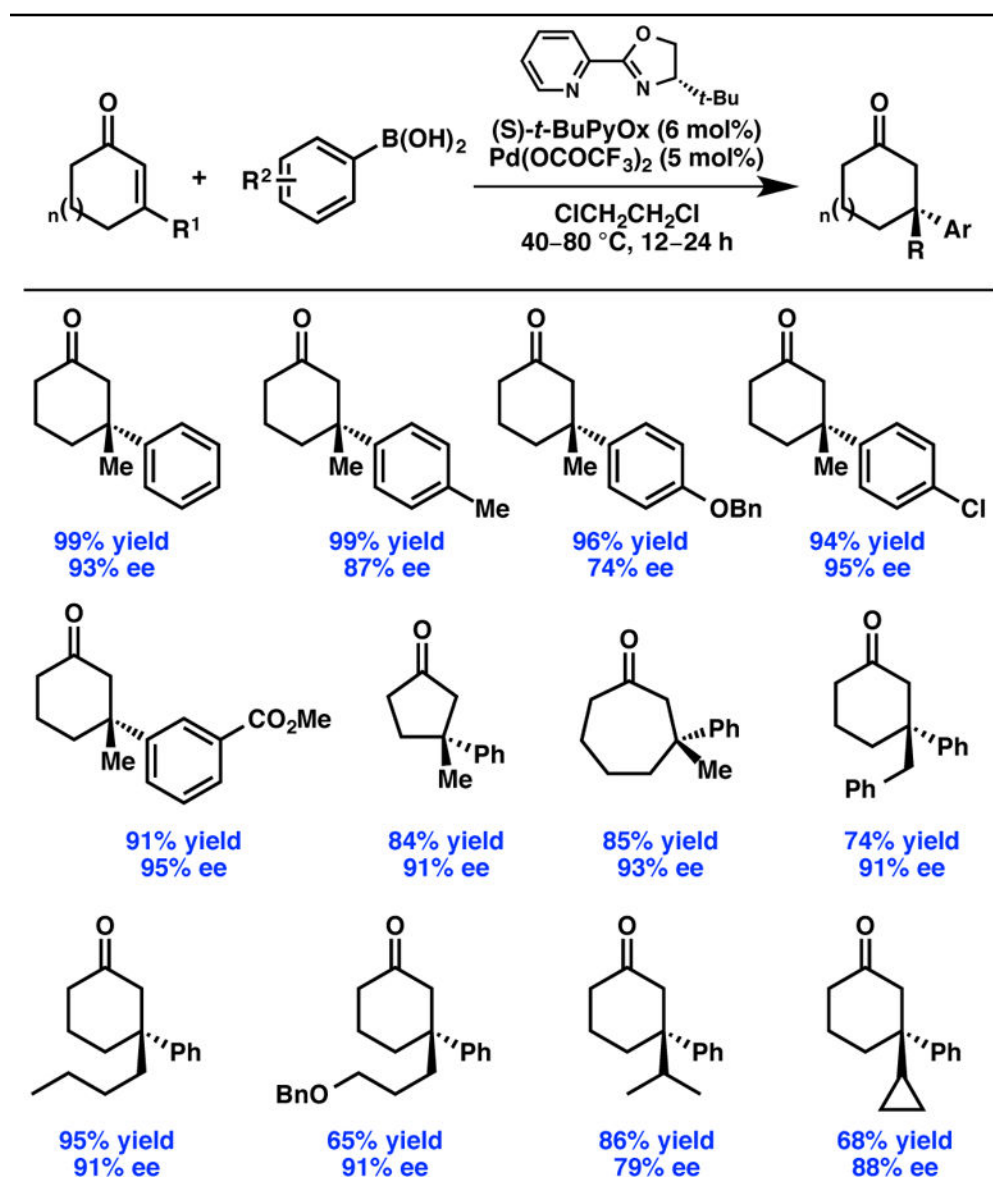


Table 3.

Increased yields under new reaction conditions.

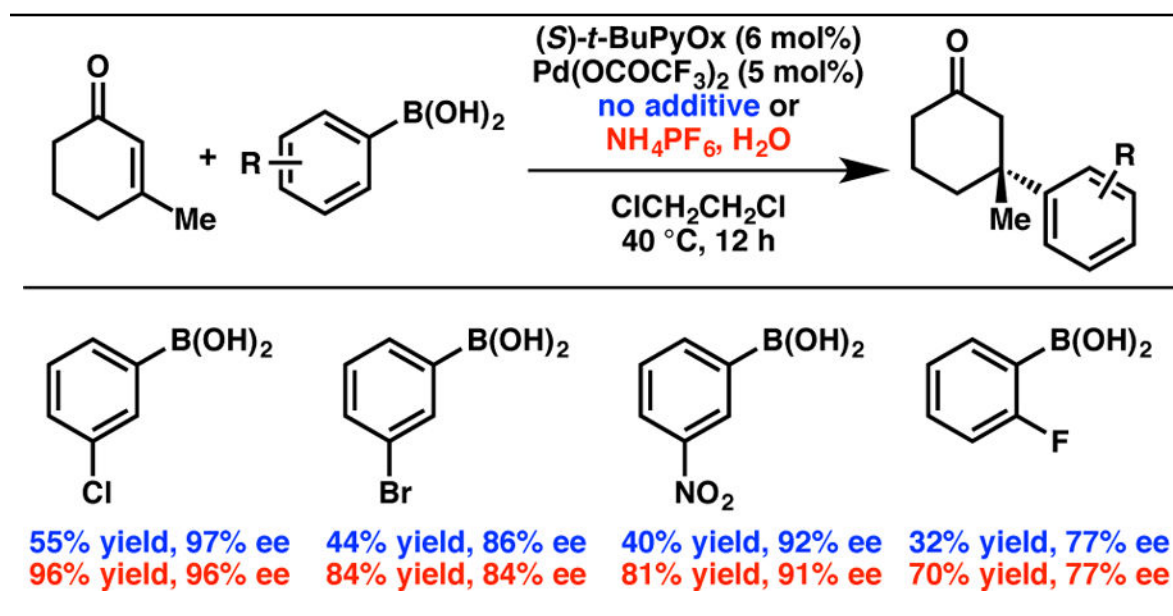


Table 4.

Enantioselective allylic alkylation of cyclic ketone enolates.

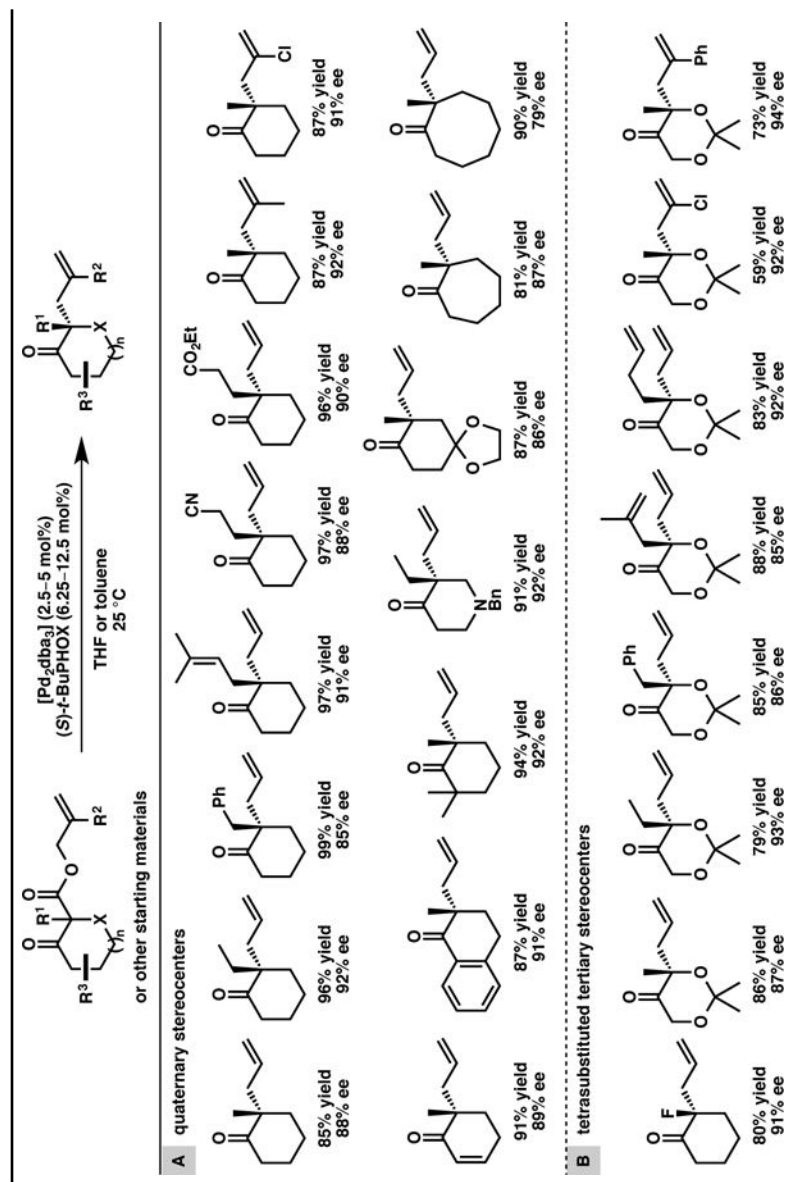




Table 5.

Enantioselective allylic alkylation of cyclobutanone and lactam enolates.

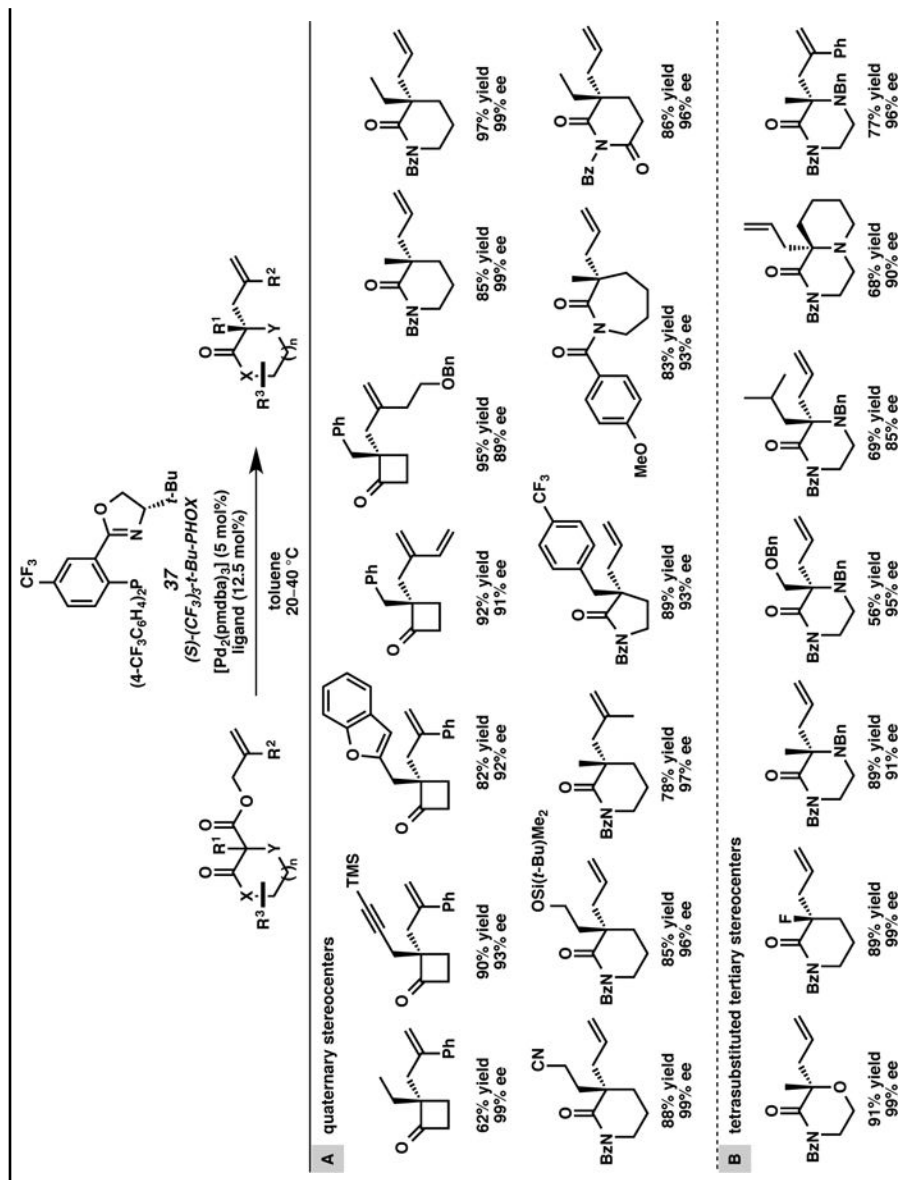


Table 6.

Selected substrates of Ir-catalyzed allylic alkylation of cyclic  $\alpha$ -substituted  $\beta$ -ketoesters.

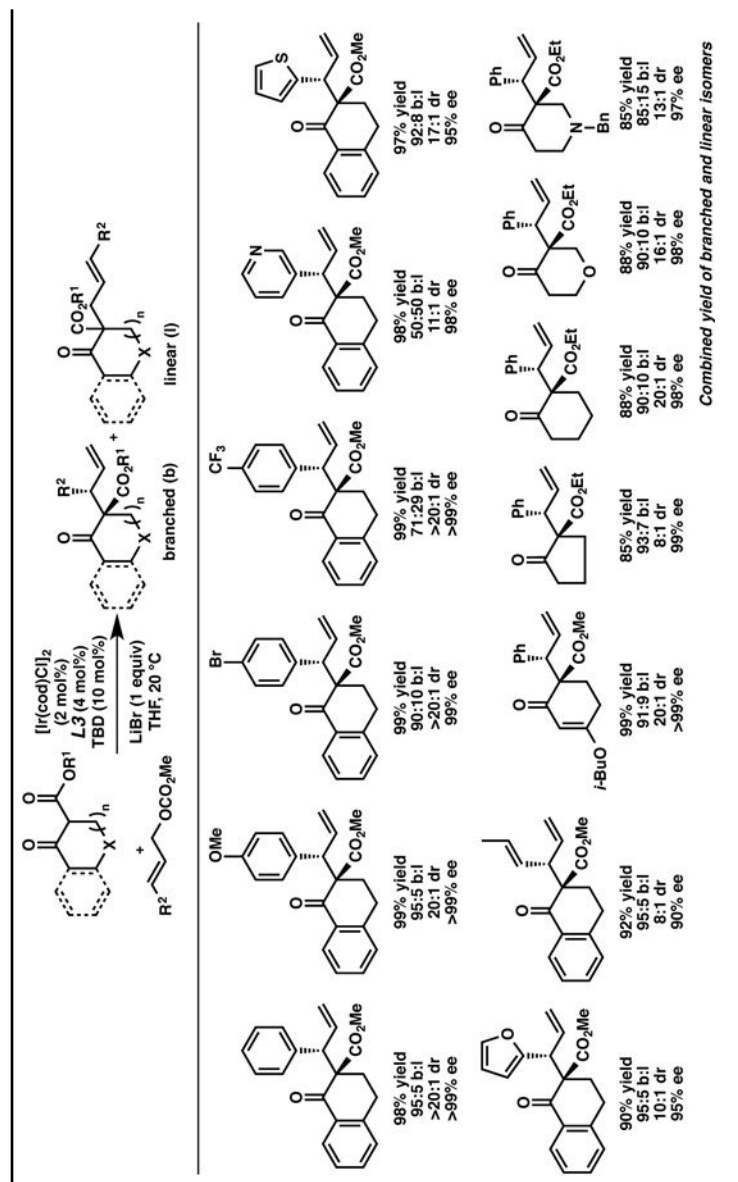


Table 7.

Selected examples of Ir-catalyzed allylic alkylation of acyclic  $\alpha$ -substituted  $\beta$ -ketoesters.

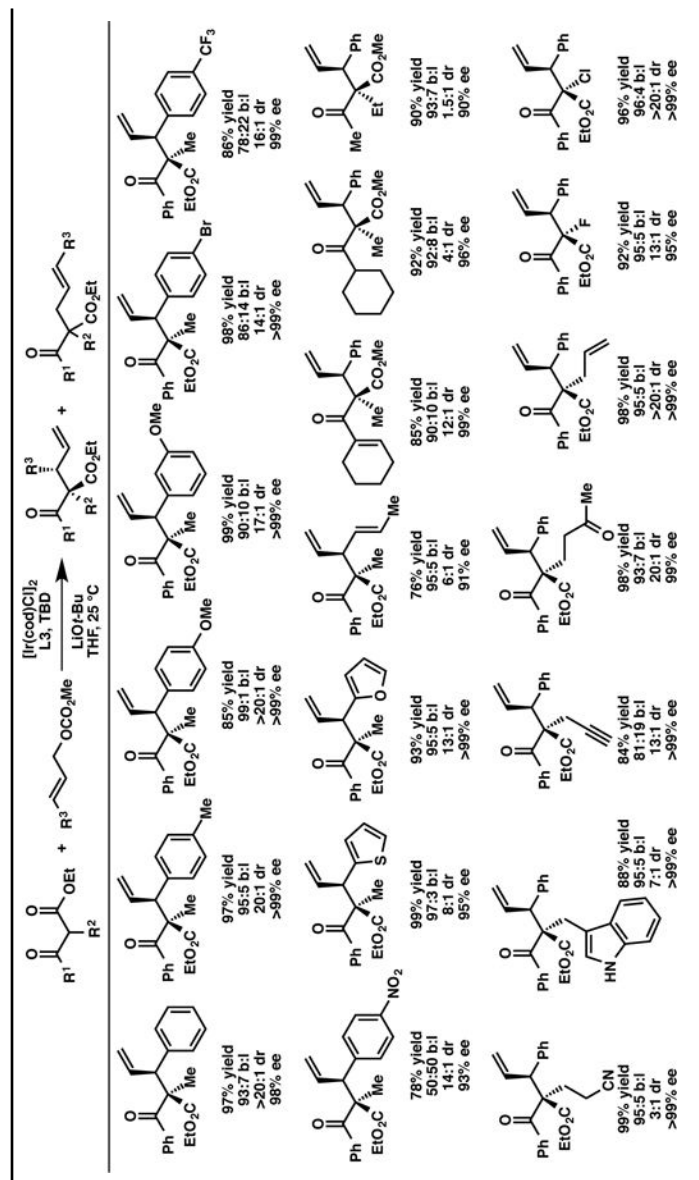
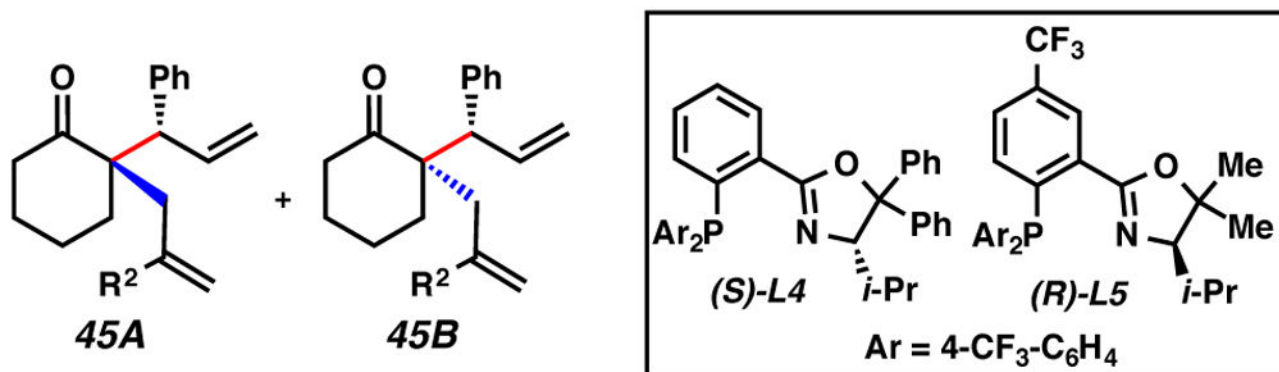
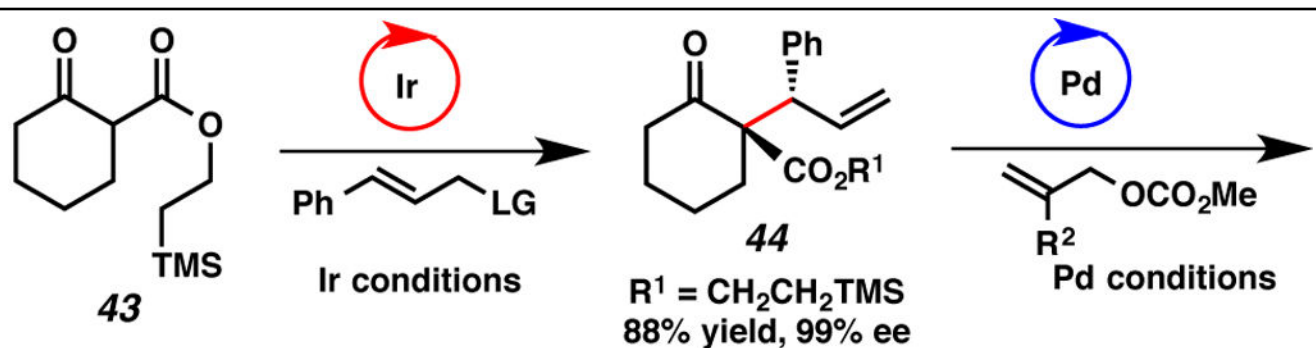


Table 8.

Sequential allylic alkylation catalyzed by iridium and palladium complexes.



entry	ligand	R <sup>2</sup>	dr ( <b>45A</b> : <b>45B</b> )	yield (%)
1	<b>L4</b>	H	1:8	91
2	<b>L5</b>	H	18:1	85
3	<b>L5</b>	Ph	13:1	87
4	<b>L5</b>	Me	12:1	80

Ir conditions: [Ir(cod)Cl]<sub>2</sub> (2 mol%), **L3** (4 mol%), TBD (10 mol%), LiBr (1 equiv), in THF at 25 °C.

Pd conditions: Pd<sub>2</sub>(dba)<sub>3</sub> (5 mol%), ligand (12.5 mol%), TBAT (1.2 equiv), allyl carbonate (1.2 equiv), in THF at 25 °C.