

# Catalytic Enantioselective Construction of Quaternary Stereocenters: Assembly of Key Building Blocks for the Synthesis of Biologically Active Molecules

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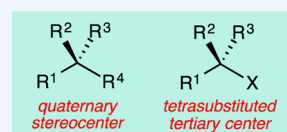
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**CONSPECTUS:** The ever-present demand for drugs with better efficacy and fewer side effects continually motivates scientists to explore the vast chemical space. Traditionally, medicinal chemists have focused much attention on achiral or so-called "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-halooxindoles, 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 phosphinooxazoline 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.



## 1. INTRODUCTION

As humanity settles into the second decade of the 21st 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,

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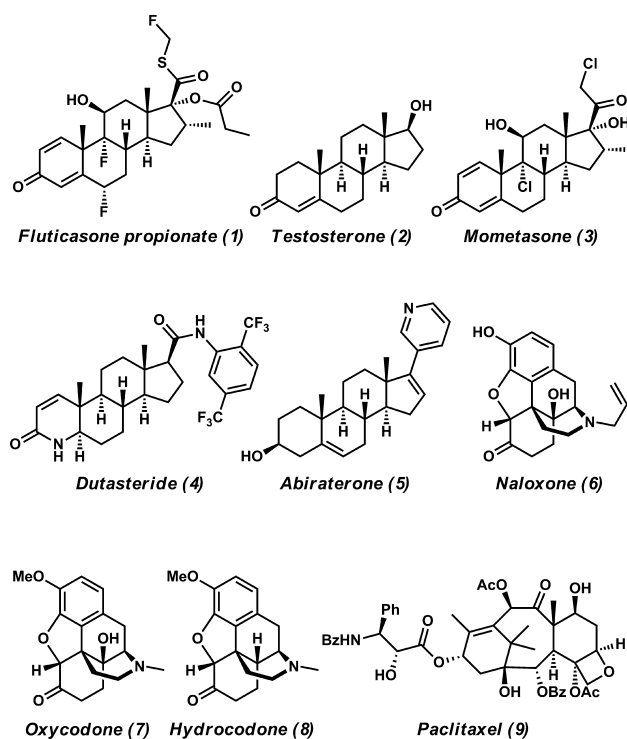
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complex small molecules that will allow medicinal chemists to explore new molecular space with functional compounds having better properties.

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



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

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.

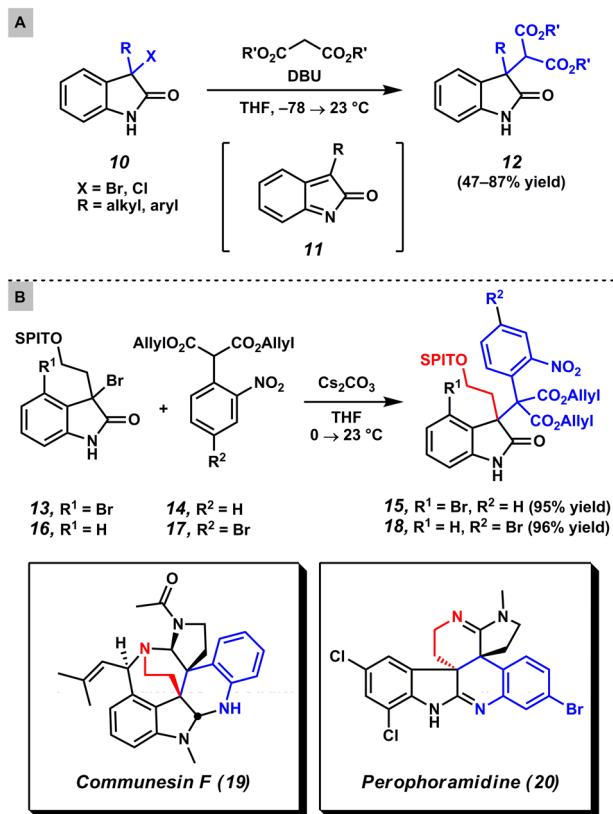
During the past decade, our research group has strategically tackled this problem by implementing an array of orthogonal approaches. The most well studied tactics that have emerged from our laboratories involve the alkylation of 3-haloindole electrophiles, the conjugate addition of boronic acids to cyclic 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 SYNTHESIS 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 nontraditional 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-haloindoles 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 counterion such as  $SbF_6^-$  (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 ones that

Scheme 1. Alkylations of 3-Halooxindoles



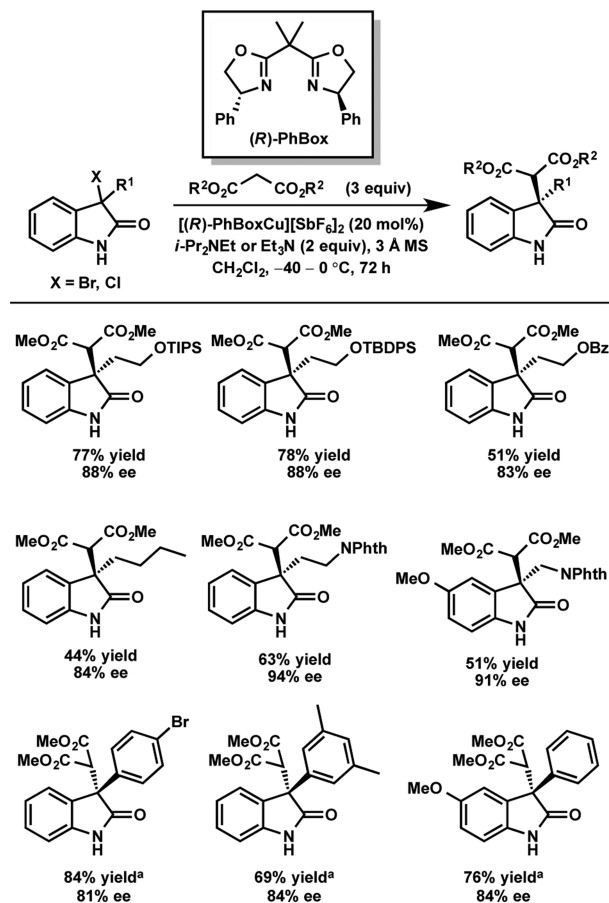
allows the preparation of both C3-alkyl and C3-aryl quaternary oxindoles with a single catalyst system.

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).

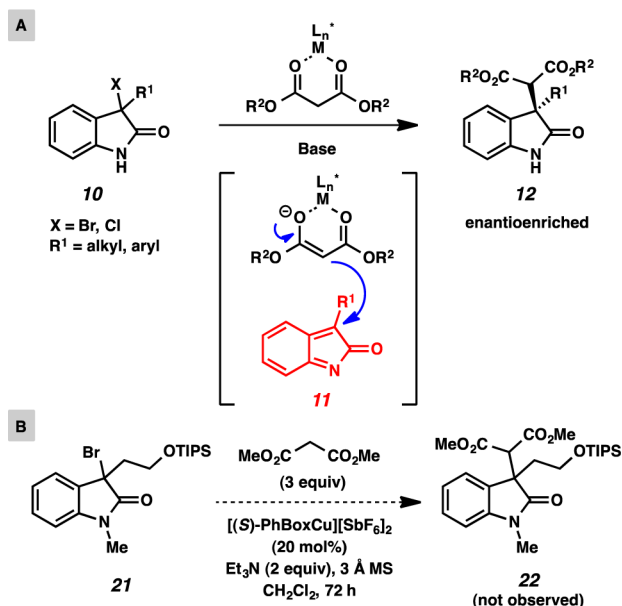
### 3. PALLADIUM-CATALYZED ASYMMETRIC CONJUGATE ADDITION OF ARYLBORONIC ACIDS TO CYCLIC ENONES TO FURNISH BENZYLIC QUATERNARY CENTERS

Although the alkylation of malonate nucleophiles to halo-oxindoles 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 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 tetraarylbates and arylboroxines could add to  $\beta,\beta$ -disubstituted enones to deliver  $\beta$ -quaternary ketones.<sup>20</sup> From a practical

Table 1. Enantioselective Alkylation of 3-Halooxindoles

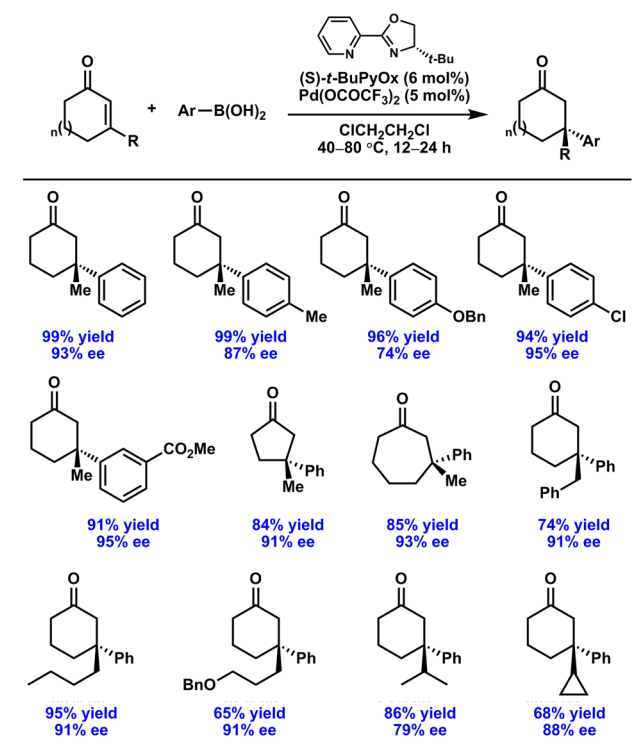


<sup>a</sup>Used 3-aryl-3-chlorooxindoles as substrates and (*S*)-PhBox as ligand.

Scheme 2. Alkylations of 3-Halooxindoles via Reactive Prochiral Indolone **11**

standpoint, using commercially available arylboronic acids as nucleophiles will make conjugate addition a much more valuable method for quaternary stereocenter generation. Additionally, the ultrahigh cost of rhodium can often be prohibitive. As a remedy for

Table 2. Asymmetric Addition of Arylboronic Acids to 3-Substituted Cyclic Enones



Scheme 3. Large Scale Conjugate Additions

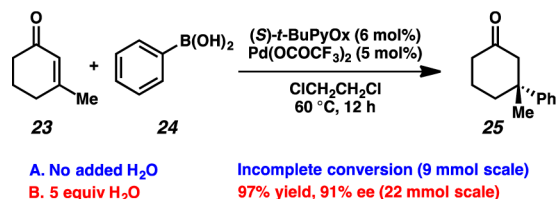
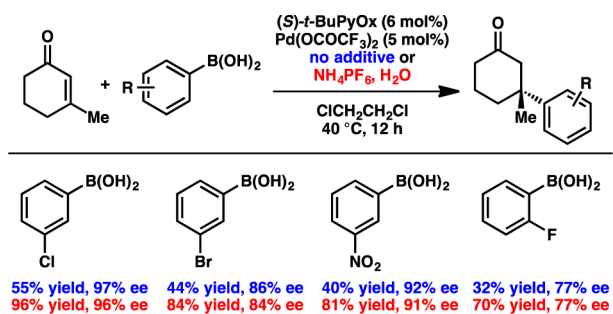


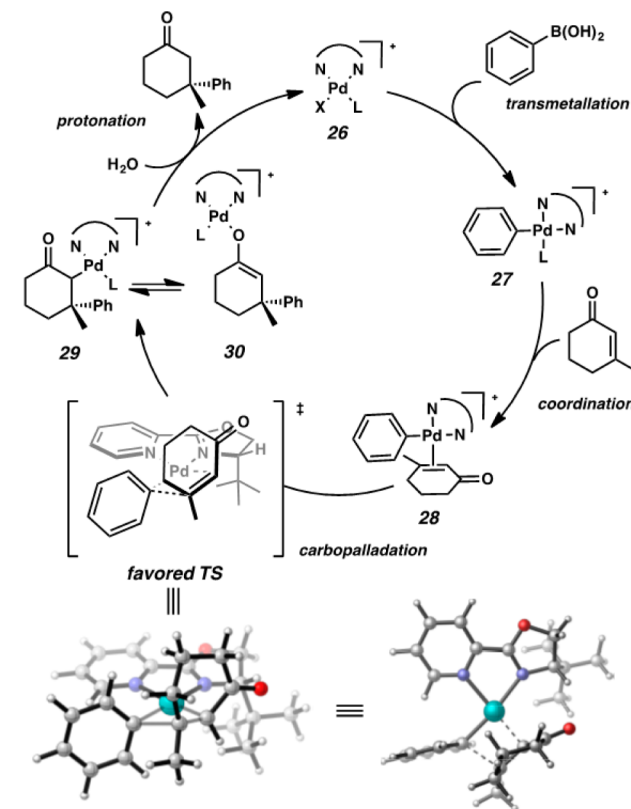
Table 3. Increased Yields under New Reaction Conditions



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

Scheme 4. Mechanistic Rationale for the Asymmetric Conjugate Addition



of reaction parameters and discovered that a combination of easily accessible chiral pyridinoxazoline (PyOx) ligand, a commercial palladium(II) trifluoroacetate precatalyst, and 1,2-dichloroethane as solvent provided the desired β-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, five-, six-, and seven-membered cyclic enones are all competent substrates for the reaction. Enones bearing more complex substituents at the β-position also undergo conjugate addition smoothly to afford the corresponding β-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 materials (Scheme 3). With 5 equiv of water, a 22 mmol scale reaction proceeded smoothly to furnish 3-methyl-3-phenylcyclohexanone (**25**) 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

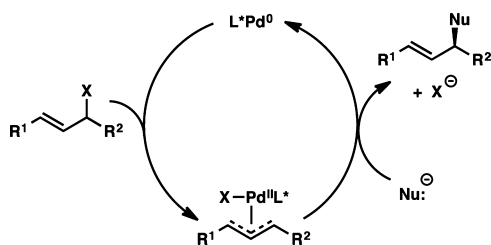
substrate into the aryl–metal bond, and protonolysis of the resulting palladium-enolate **30**. These investigations suggest that the bond-forming palladium species is an arylpalladium(II) cation (**28**), and enantioselectivity is governed by steric repulsions between the *t*-Bu group of the chiral ligand and the  $\alpha$ -methylene hydrogens of the cyclohexenone substrate.

#### 4. PALLADIUM-CATALYZED ENANTIOSELECTIVE ALLYLIC ALKYLATION OF PROCHIRAL ENOLATES

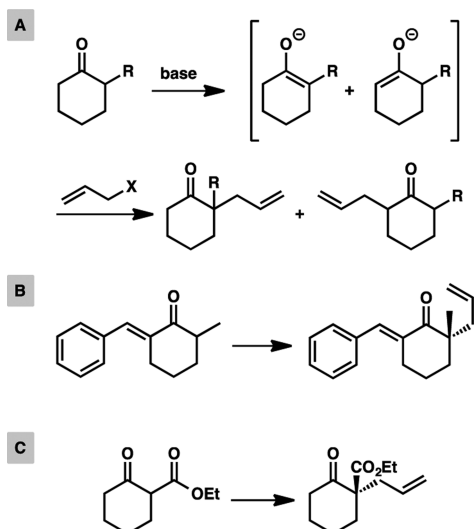
The first two sections of this manuscript discuss benzylic quaternary centers, yet a potentially greater challenge to asymmetric catalysis lies in bond forming chemistries that have no proximal aromatic groups. It is often the case that asymmetric reactions may function at benzylic positions and then 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 multistep 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).

Scheme 5. General Mechanism of Pd-Catalyzed Asymmetric Allylic Alkylation

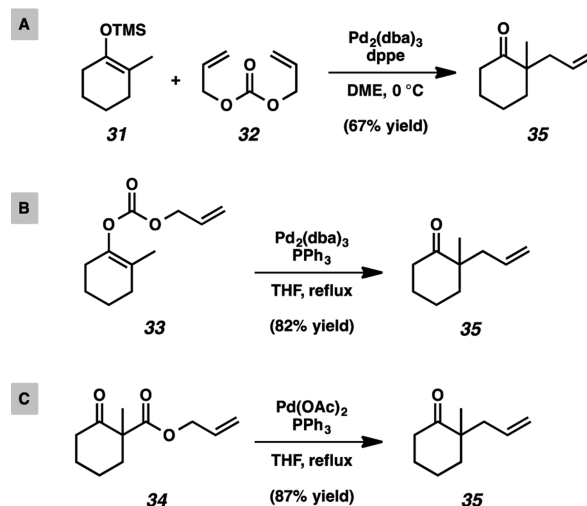


Scheme 6. Challenges in Alkylation of Nonsymmetrical Ketones

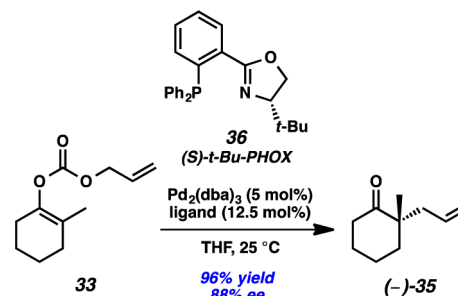


The pioneering earlier works of Trost,<sup>27</sup> Helmchen,<sup>28</sup> and others focused mainly on prochiral allyl electrophiles. Although this reaction mode enjoys success with a broad range of substrates and has found numerous applications in natural products

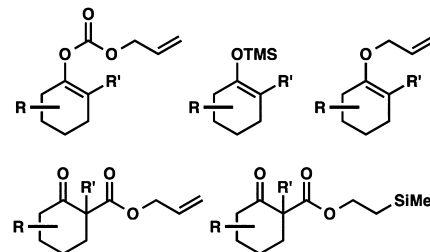
Scheme 7. Tsuji Allylic Alkylation



Scheme 8. Discovery of an Enantioselective Catalyst System for the Asymmetric Tsuji Allylic Alkylation



#### Masked enolate synthons:



#### Allylic Electrophiles:

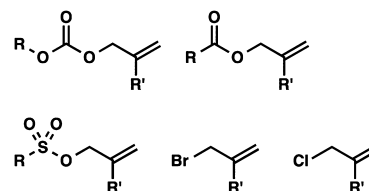


Figure 2. Substrate possibilities for the enantioselective alkylation reaction.

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

Table 4. Enantioselective Allylic Alkylation of Cyclic Ketone Enolates

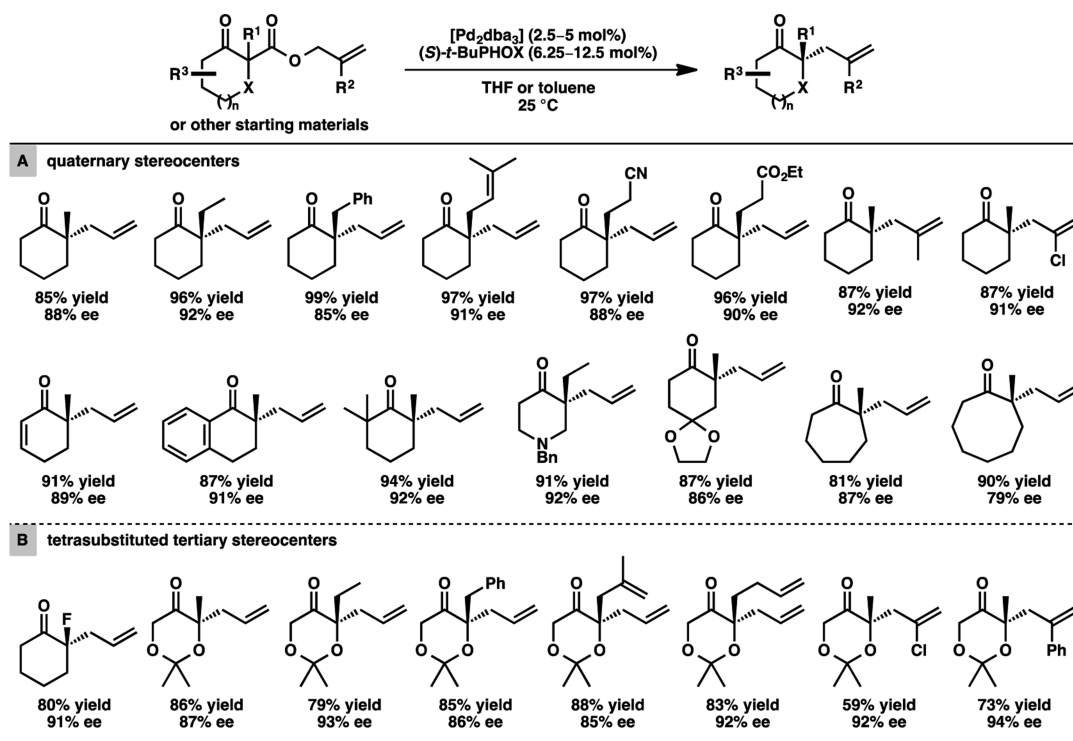
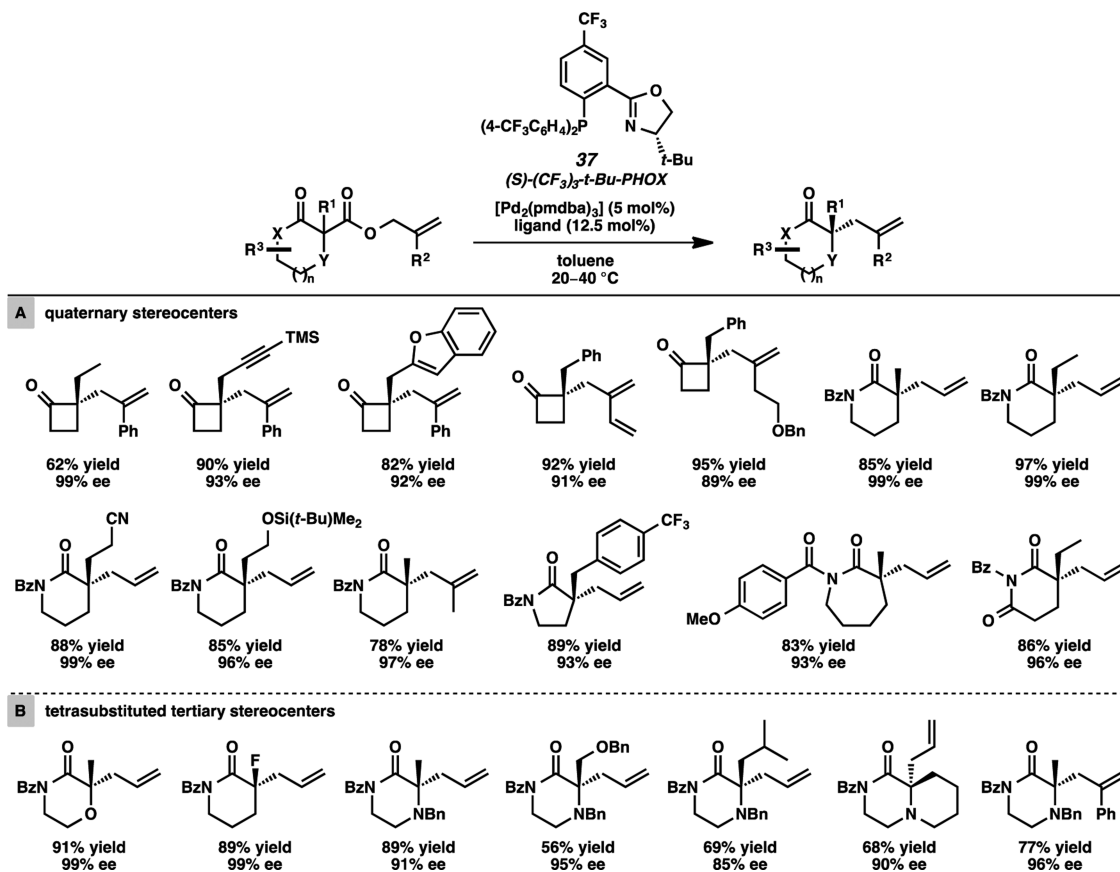


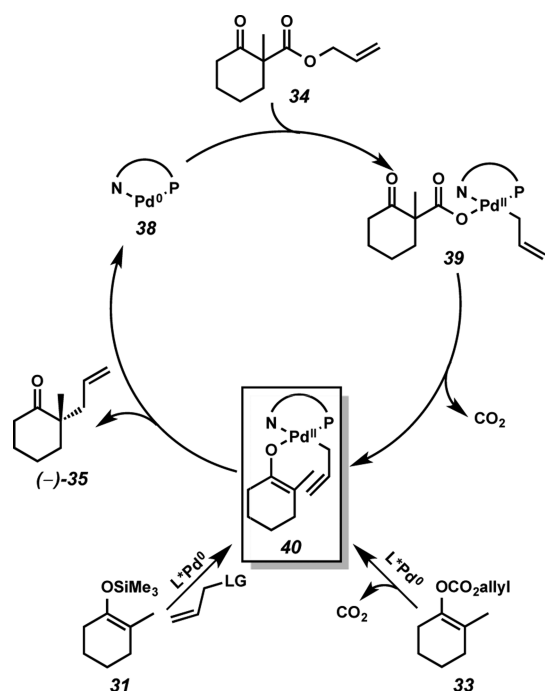
Table 5. Enantioselective Allylic Alkylation of Cyclobutanone and Lactam Enolates



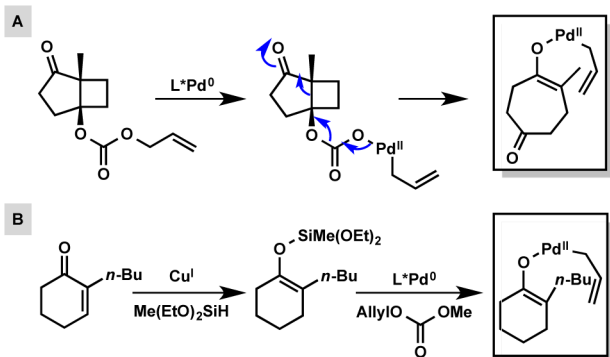
of such nucleophiles is a tetrasubstituted enolate, generated by deprotonation of a carbonyl compound. However, position-selective enolate generation can be particularly challenging if the carbonyl compound bears multiple, similarly acidic  $\alpha$ -protons.

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

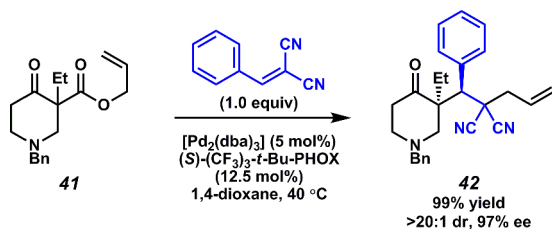
Scheme 9. Proposed Mechanism for Palladium-Catalyzed Allylic Alkylation



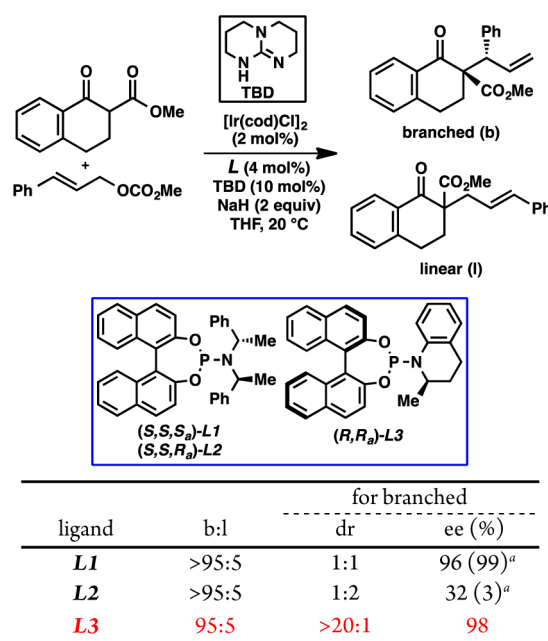
Scheme 10. Generation of Palladium Enolate Intermediates from Other Starting Materials



Scheme 11. Asymmetric Enolate Alkylation Cascade with Different Electrophiles



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  $pK_a$  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.

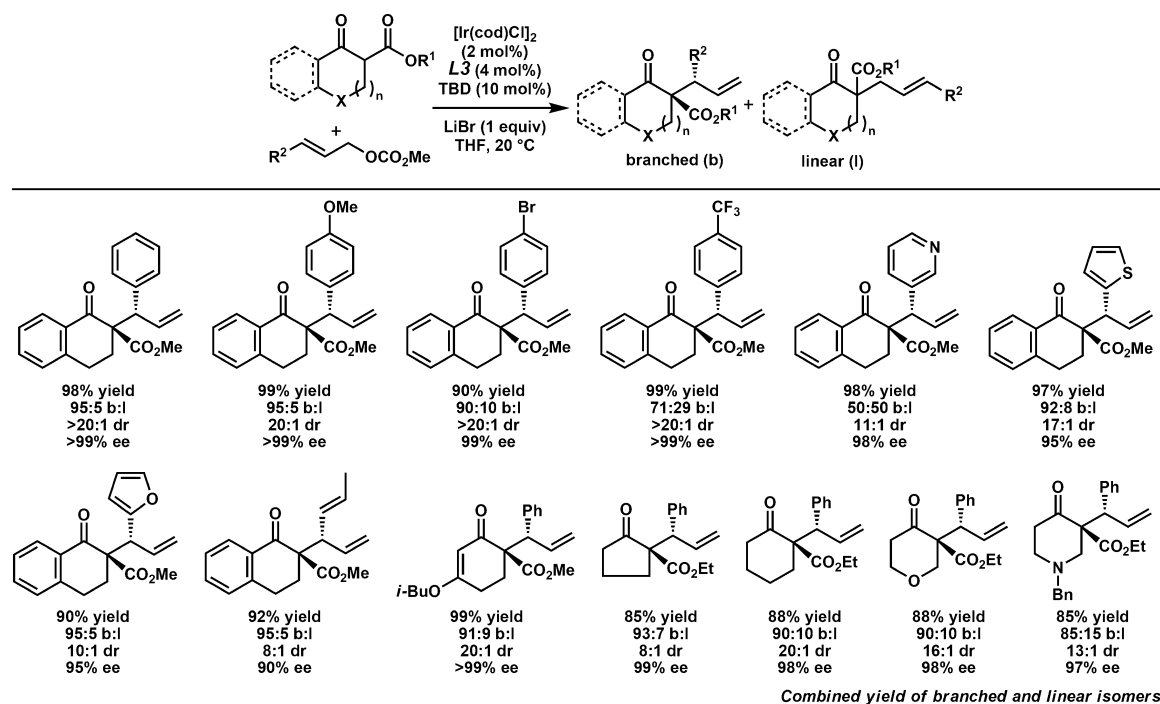
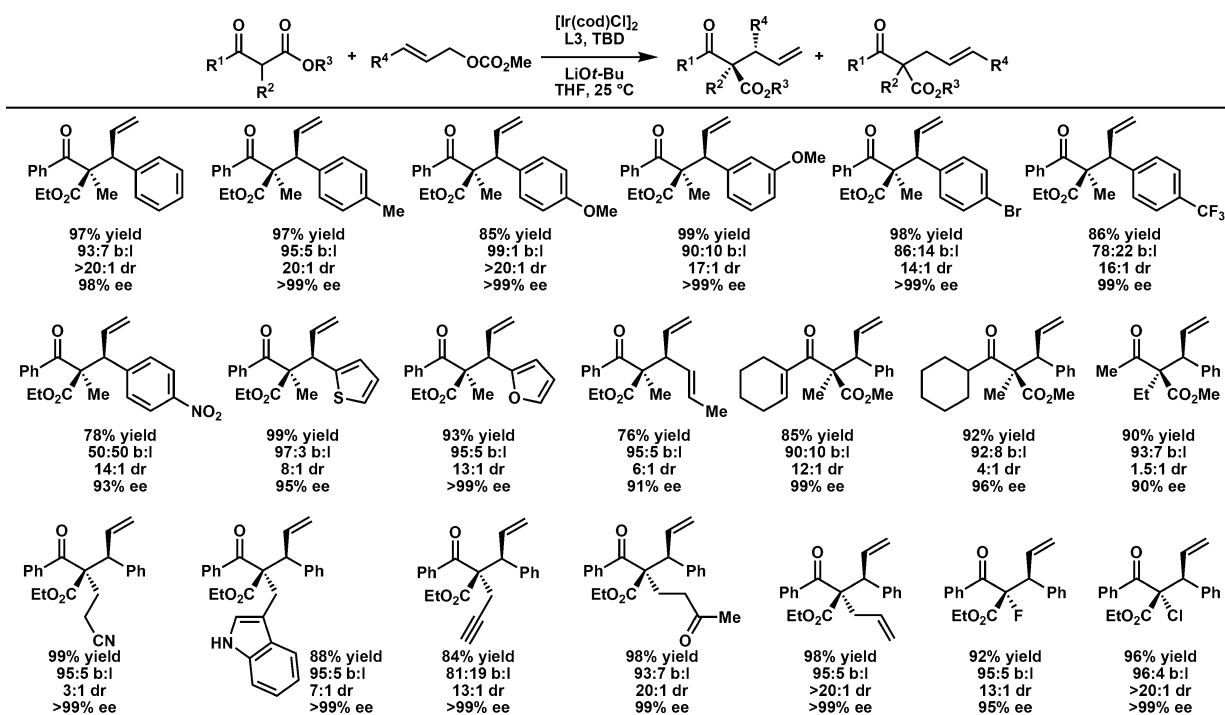
Scheme 12. Ir-Catalyzed Allylic Alkylation of Cyclic  $\alpha$ -Substituted  $\beta$ -Ketoesters

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

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 nonenantioselective 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,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 trimethylsilyl ethyl keto esters can serve as nearly equivalent masked enolate substrates (Figure 2). The electrophilic allyl unit

Table 6. Selected Substrates of Ir-Catalyzed Allylic Alkylation of Cyclic  $\alpha$ -Substituted  $\beta$ -KetoestersTable 7. Selected Examples of Ir-Catalyzed Allylic Alkylation of Acyclic  $\alpha$ -Substituted  $\beta$ -Ketoesters

can bear carbonates, acetates, sulfonates, and in some instances even halides as the leaving group. The great flexibility in substrate choice allows for strategic implementation in the context of multistep 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, at 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, 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 laboratories 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 deacylative 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 the desired reactivity and produced enantioenriched cyclic ketones bearing adjacent quaternary and tertiary stereocenters (Scheme 11).<sup>44</sup>

## 5. IRIIDIUM-CATALYZED ALLYLIC ALKYLATION FOR THE CONSTRUCTION OF VICINAL QUATERNARY AND TERTIARY STEREOCENTERS

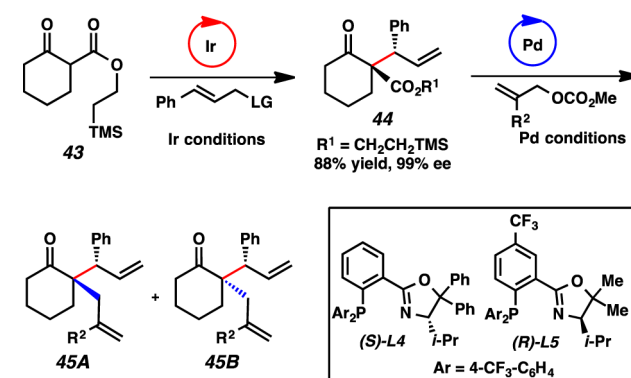
Based on the intriguing diastereochemical issues encountered in the Pd-enolate trapping chemistry, we became interested in other methods for direct generation of vicinal quaternary–tertiary relationships. Recently, by employing prochiral  $\alpha$ -substituted cyclic  $\beta$ -ketoester enolates as nucleophiles, 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 [Ir(cod)Cl]<sub>2</sub> 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 [Ir(cod)Cl]<sub>2</sub>·*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 Pd<sub>2</sub>(dba)<sub>3</sub> 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

**Table 8. Sequential Allylic Alkylation Catalyzed by Iridium<sup>a</sup> and Palladium<sup>b</sup> Complexes**



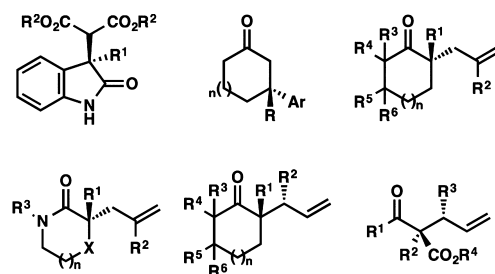
entry	ligand	R <sup>2</sup>	dr (45A/45B)	yield (%)
1	L4	H	1:8	91
2	L5	H	18:1	85
3	L5	Ph	12:1	87
4	L5	Me	13:1	70

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

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



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

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.

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### Notes

The authors declare no competing financial interest.

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**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 laboratories 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.

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