

The Synthesis of Molecules Containing Quaternary Stereogenic Centers via the Intramolecular Asymmetric Heck Reaction

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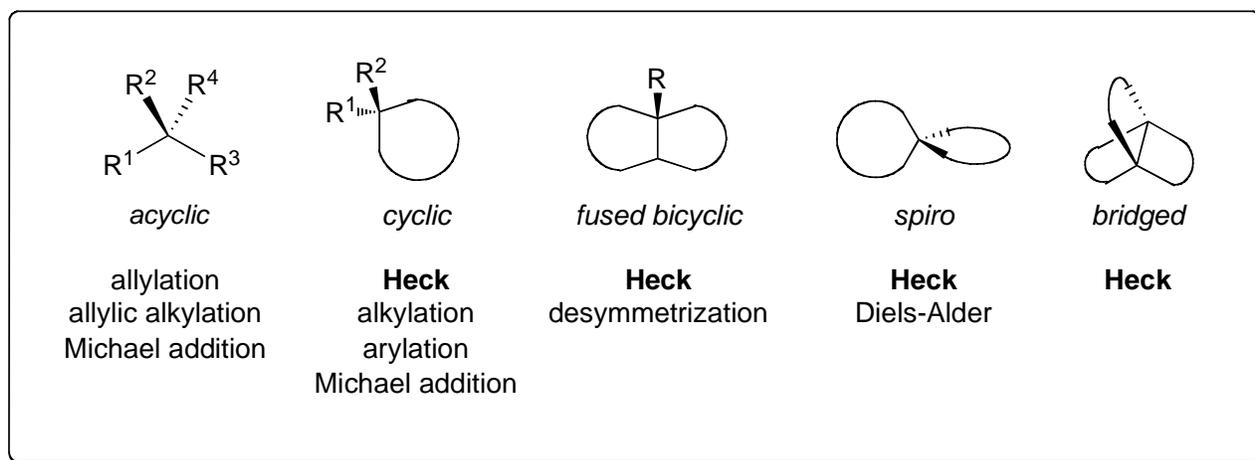
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INTRODUCTION

The enantioselective synthesis of compounds containing quaternary stereocenters continues to be a challenging endeavor and is a field of intense interest and development.^{1,2,3,4,5} From the perspective of methods development, the asymmetric synthesis of compounds containing quaternary stereocenters poses a distinct challenge due to the sterically congested environment in which C-C bonds must be formed and stereochemical information must be transferred. Existing asymmetric methods have been applied successfully in desymmetrization processes that transform prochiral quaternary centers into stereodefined quaternary centers. However, for processes in which a quaternary stereocenter is created directly via a C-C bond forming reaction, only a few asymmetric reactions have been fruitful.

The diversity in the array of methods that exist for the synthesis of compounds containing quaternary stereocenters is necessitated in part because of the number of distinct quaternary stereocenter architectures that are possible (Scheme 1). The construction of acyclic quaternary stereocenters is particularly challenging due to the number of degrees of freedom associated with these structures. However, promising results for the construction of these stereocenters via allylation,⁶ allylic alkylation,⁷ and Michael addition⁸ have been reported recently. For the synthesis of cyclic quaternary stereocenters a number of methods have been employed successfully including the intramolecular Heck reaction,⁹ alkylation,¹⁰ arylation,¹¹ and Michael addition¹². Fused bicyclic quaternary stereocenters are generally accessed via the desymmetrization of a prochiral quaternary center. In this regard, theoretically any

SCHEME 1. Leading methods for the synthesis of quaternary stereocenters



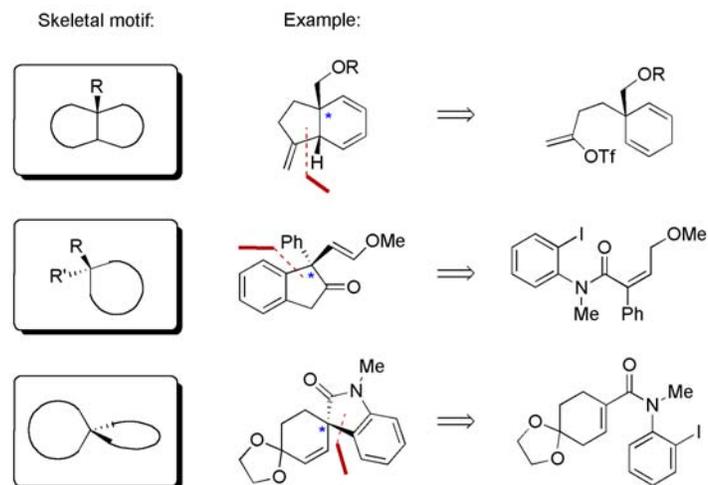
asymmetric bond forming reaction could be employed, however, use of the intramolecular Heck reaction has attracted particular attention. For the synthesis of spiro and bridged quaternary stereocenters the intramolecular Heck reaction has likewise found wide application.¹³

Although Scheme 1 illustrates that all quaternary stereocenter architectures can be accessed via a catalytic asymmetric method, the design of a synthesis for a compound containing a quaternary stereocenter is not straightforward. For many of the methods described above the substrate scope remains largely unexplored and very few of the methods have been applied in the context of a total synthesis. Additionally, for many of these methods the choice of catalyst and reaction condition has not been generalized, and optimization which is not straightforward is required before useful yields and enantioselectivities are obtained. Finally, for methods such as Michael addition or Diels-Alder cycloaddition, reaction times are often prohibitively long.

With the above considerations, it is not surprising that the asymmetric intramolecular Heck reaction has attracted considerable interest as a general method for the construction of molecules containing cyclic or spiro quaternary centers (Scheme 2).^{13,14,15} In these reactions BINAP is often a sufficient ligand, and enantiomeric ratios $\geq 9:1$ are often achieved. This abstract will present the

mechanistic foundation of the Heck reaction, followed by selected case studies on the stereo-controlling elements of the asymmetric intramolecular Heck reaction as a window into the complex nature of this reaction. Finally, as a demonstration of the remarkable simplifying power of the Heck transform, applications of the intramolecular Heck reaction in the total synthesis of molecules containing quaternary stereocenters will be presented.

SCHEME 2. Carbon frameworks directly accessed by the intramolecular asymmetric Heck reaction



THE HECK REACTION

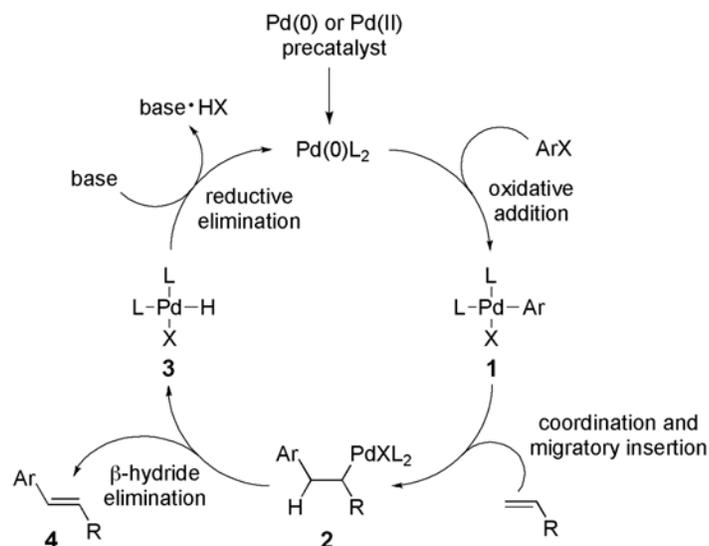
General mechanism

The Heck reaction describes the palladium-mediated coupling of an aryl or vinyl halide or triflate with an alkene. A simplified scheme depicting the major steps of the Heck catalytic cycle for the reaction of an aryl halide is presented in Scheme 3. A Pd(0) species first inserts via oxidative addition into the carbon-halogen bond to yield a σ -arylpalladium(II) complex (**1**). Coordination of the alkene and

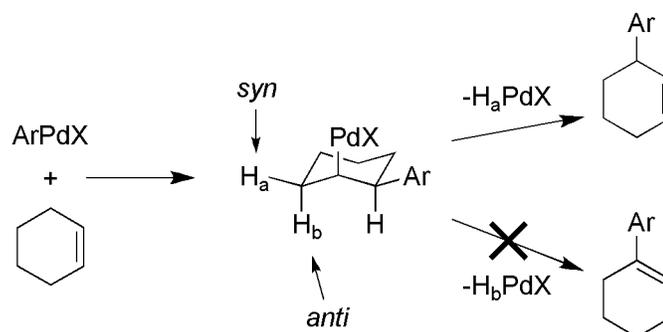
subsequent migratory insertion then follows to afford a σ -alkylpalladium(II) complex (**2**). Most commonly, the catalytic cycle proceeds by a concerted *syn* elimination of the β -hydrogen to form a palladium hydride species (**3**) and release the olefin product (**4**). Heck reactions of acyclic olefins are complicated by the issue of regioselectivity in this step as there is often more than one β -hydrogen available for elimination. However, intramolecular Heck reactions are often performed with cyclic alkenes for which the issue of regioselectivity does not exist because only one *syn* β -hydrogen is available for elimination (Scheme 4). A stoichiometric amount of base is needed to quench the acid generated by reductive elimination of the palladium hydride species (**3**).

It is widely accepted that the Heck reaction can also proceed via a second mechanistic pathway, termed "cationic" because of the formal positive charge assigned to the palladium species prior to binding of the olefin (Scheme 5).¹⁶ This pathway is distinguished from the "neutral" pathway by the dissociation of an anion (halide or triflate) from the palladium center following oxidative addition. When triflates are employed in the Heck reaction, this process occurs spontaneously due to the lability of the TfO-Pd bond.¹⁷ When halides are used, this process can be promoted through the addition of either Ag^+ or Tl^+ salts (halide scavengers) which abstract the halide

SCHEME 3. Key steps in the Heck catalytic cycle

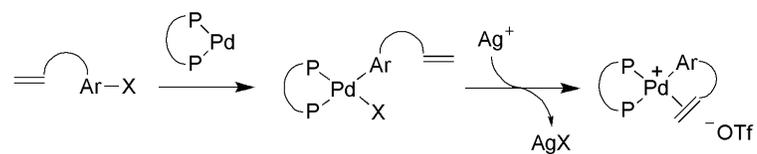


SCHEME 4. Paths for β -hydride elimination

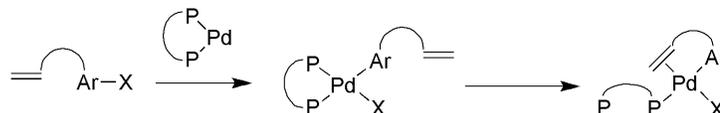


SCHEME 5. Two mechanistic pathways for alkene coordination

"Cationic" pathway:



"Neutral" pathway:



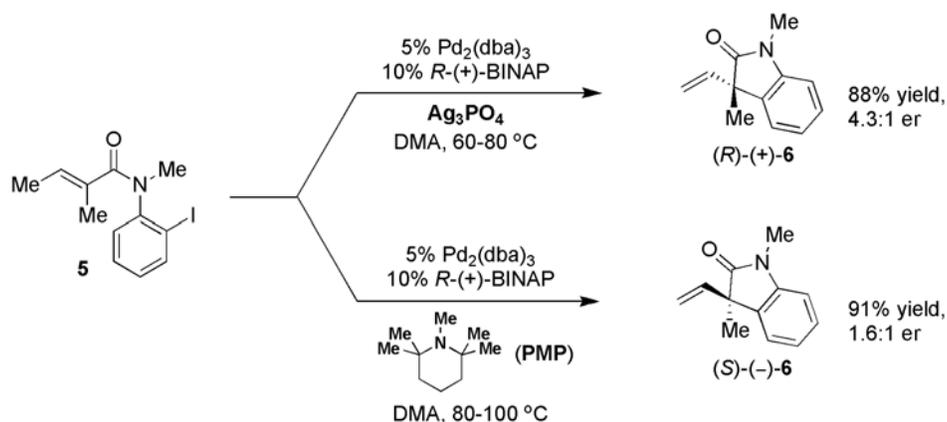
from the palladium species. In cases where the bidentate chiral ligand is weakly complexed with palladium, the “cationic” pathway generally leads to higher enantioselectivity, presumably because a coordination site to accommodate the alkene is made available without the need to partially dissociate the chiral ligand (Scheme 5). However, when BINAP is used as the chiral ligand evidence suggests that the phosphine ligands do not dissociate (see below).

Models for stereocontrol

Because substrate-specific interactions strongly influence of asymmetric induction in the intramolecular Heck reaction, a generalized predictive model for the stereochemical course of this reaction does not exist. In the intramolecular desymmetrizing Heck reaction the stereodefining step is generally agreed to be the migratory insertion step. Although a speculative model to rationalize the stereochemical course of this reaction has been proposed,¹⁸ even the desymmetrizing Heck reaction has been observed to be influenced by unexpected substrate-specific interactions.¹⁹ For cases in which the quaternary center is formed during the Heck cyclization, the factors that influence the stereochemical outcome of the reaction are often quite complicated.

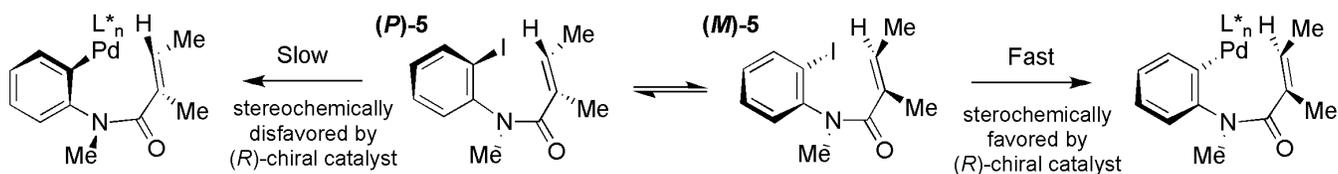
As an example of the subtle influences that affect the stereochemical outcome of the intramolecular asymmetric Heck reaction, the case study on the asymmetric Heck cyclization of *o*-iodoacrylanilides is presented. Intriguingly, the stereochemical outcome of this reaction is dependent on whether or not a silver salt is used in the reaction (Scheme 6).²⁰ Furthermore, by increasing the reaction temperature from 60 °C to 80 °C, higher enantioselectivity was observed.²¹ To rationalize the observed temperature effect, Stephenson and co-workers proposed a model in which the chiral palladium catalyst preferentially adds via oxidative addition into one of the two atropisomers of **5** (Scheme 7). In this model, oxidative addition is the stereodefining step. At low temperature the racemization of **5** is slow, and as (*M*)-**5** is consumed in the reaction, (*P*)-**5** also begins to react. At elevated temperature the enantiomers

SCHEME 6. The stereochemical outcome of the Heck reaction can be influenced by additives



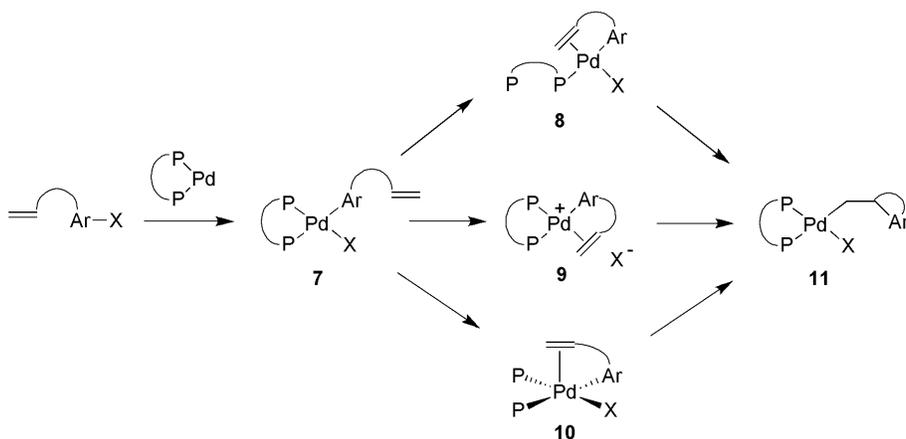
of **5** are in rapid equilibrium and a dynamic kinetic resolution process is operative. As evidence in support of this model, Curran and coworkers reported that the reaction of enantiopure **5** with an achiral palladium catalyst at room temperature affords **6** with a 5.7:1 er and that the rotational barrier for racemization of **5** is 26.0 kcal/mol.²²

SCHEME 7. A kinetic resolution mechanism is proposed in the reaction of *o*-iodoacrylanilides



However, the model presented in Scheme 7 does not address the role of Ag_3PO_4 in the reaction of **5** to **6**. As indicated by the observed stereo-divergence of the reaction between “neutral” and “cationic” conditions, the migratory insertion step must also play a role in the stereo-outcome of this reaction. To account for this divergence, Overman and Poon examined three possible mechanisms for the migratory insertion step in the “neutral” pathway (Scheme 8).²³ In a Heck cyclization similar to **5** \rightarrow **6**, enantioselectivity decreased markedly when a monocoordinate derivative of BINAP was used instead of BINAP itself, which is consistent with a reaction pathway through intermediate **8** is not operative in reactions that employ BINAP. Overman and Poon also reasoned that pathway **10** \rightarrow **11** is energetically unfavorable and that the observed stereodivergence in the reaction of **5** cannot be rationalized by pathway **7** \rightarrow **9** \rightarrow **11** due to the similarity of this pathway to that of the “cationic” mechanism. Therefore, in the asymmetric Heck reaction of *o*-iodoacrylanilides under neutral conditions, the pathway **7** \rightarrow **10** \rightarrow **9** \rightarrow **11** is proposed to be operative. In this mechanism, the approach of the alkene to the chiral palladium complex under neutral conditions is distinct from that of the cationic mechanism, and a divergence in the stereo-outcome of the reaction is therefore plausible.

SCHEME 8. Three possible mechanisms for alkene coordination in the neutral pathway



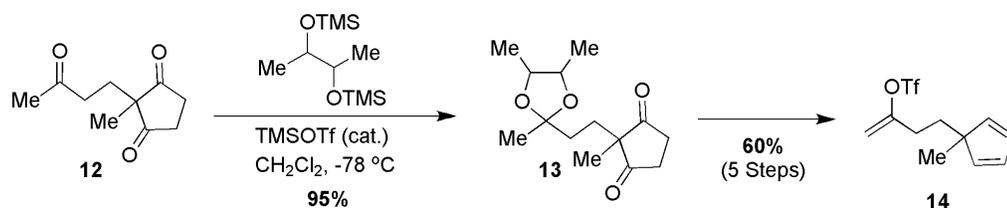
APPLICATIONS OF THE ASYMMETRIC HECK REACTION IN TOTAL SYNTHESIS

The synthesis of (-)-capnellene: Application of the desymmetrizing Heck reaction

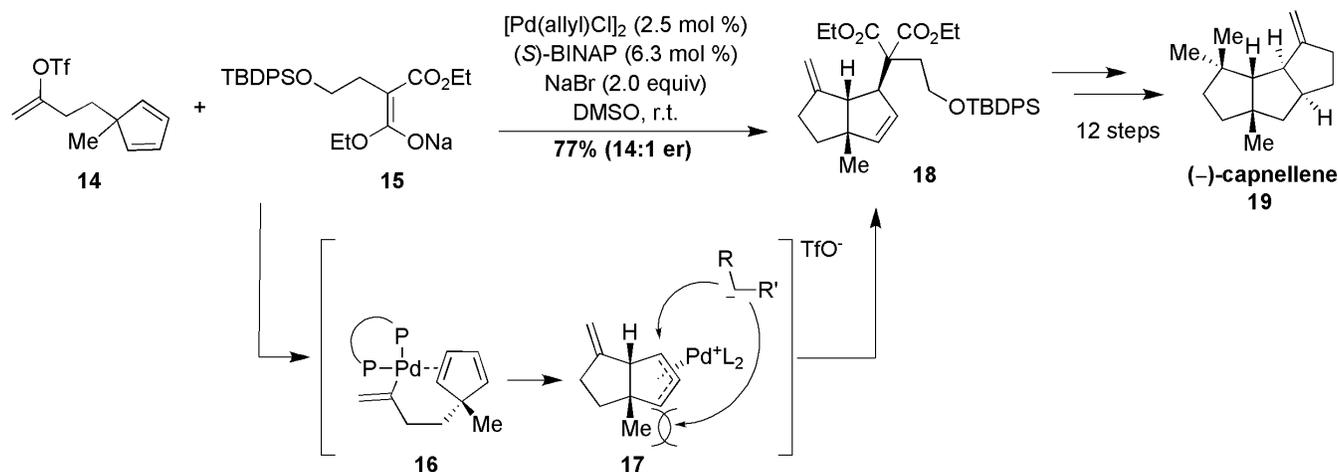
The desymmetrizing intramolecular Heck reaction has emerged as a powerful method for the synthesis of molecules containing a quaternary stereocenter derived from a prochiral precursor. Through an enantiotopic group-selective Heck cyclization, the configuration of the quaternary center is set. As a general requirement for this transformation, the enantiotopic groups must be incorporated into a cyclic framework. In an example of the application of this transform in total synthesis, Shibasaki and coworkers employed as a key step in the synthesis of (-)-capnellene (**19**) an intramolecular desymmetrizing Heck reaction in which the resulting η^3 -allyl-Pd intermediate was intercepted by a diethylmalonate enolate.

Vinyl triflate **14** was synthesized from **12** in 6 steps and 57% overall yield (Scheme 9). Next, **14** was converted to **18** in 77% yield upon exposure to Heck coupling conditions in the presence of enolate **15** (Scheme 10). In this Heck cyclization β -hydride elimination does not occur, so additional base was not required. The high enantioselectivity (14:1 er) was achieved only when NaBr was added to the reaction solution, although the role of this additive is unclear. The authors rationalize the

SCHEME 9. Synthesis of the prochiral vinyl triflate



SCHEME 10. Desymmetrizing Heck cyclization with nucleophile capture of a η^3 -allyl-palladium intermediate

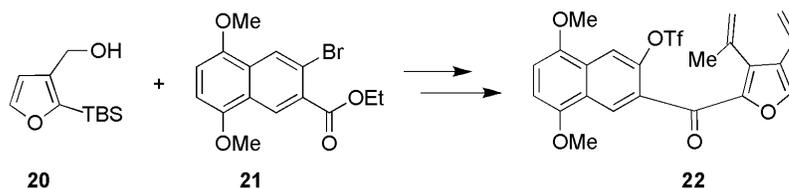


stereoselectivity in the addition of **15** by invoking the steric shielding of the methyl group of η^3 -allyl-Pd intermediate **17**. From intermediate **18** the natural product was synthesized in 12 additional steps in 20% overall yield to complete the first catalytic enantioselective synthesis of (-)-capnellene.

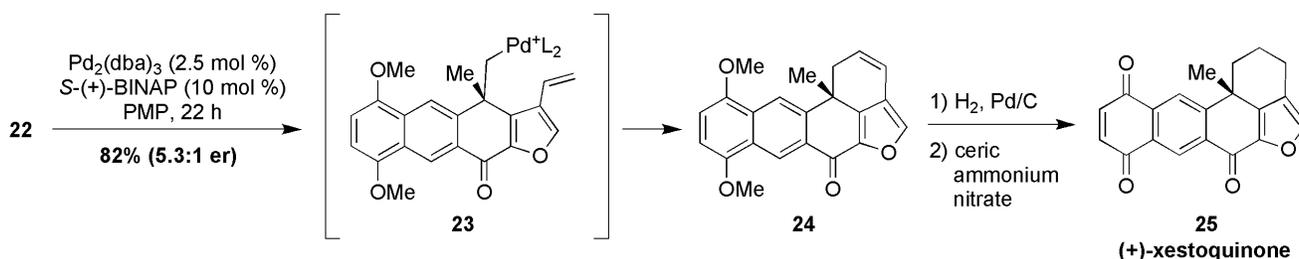
The synthesis of (+)-xestoquinone via a tandem asymmetric Heck cyclization

In the first reported asymmetric synthesis of (+)-xestoquinone (**25**), Keay and coworkers employed an elegant late-stage tandem asymmetric Heck reaction as a key step in the construction of the cyclic carbon framework.²⁴ To begin, aryl triflate **22** was synthesized in several steps from furan **20** and naphthalene **21** (Scheme 11). Upon exposure of **22** to Heck coupling conditions, **24** was obtained in 82% yield and 5.3:1 er (Scheme 12). Despite efforts to replace **22** with an aryl bromide, Heck coupling of the halide proceeded with inferior yield and enantioselectivity even following extensive optimization. A later study by Shibasaki showed that by employing a more active catalyst in conjunction with Ag-exchanged zeolites, the same enantiomeric excesses could be obtained from the Heck reaction of the aryl bromide, but the chemical yield remained low (39%).²⁵ Although the enantioselectivity obtained in this tandem Heck cyclization is modest, the complexity generated by this single reaction is impressive. From **24** only 2 additional steps were needed to access the natural product (Scheme 12).

SCHEME 11. Synthesis of the aryl triflate intermediate



SCHEME 12. The synthesis of (+)-xestoquinone via a tandem asymmetric Heck reaction



CONCLUSION

In conclusion, the intramolecular asymmetric Heck reaction is a powerful method for the synthesis of molecules containing quaternary stereocenters. Studies on the mechanistic basis for asymmetric induction in the intramolecular Heck reaction highlight the large number of parameters that influence the stereochemical course of the reaction. As a result, a generalized predictive model for stereocontrol in the intramolecular Heck reaction remains to be formulated. However, the complex nature of the Heck reaction is as intriguing as it is challenging. The use of the Heck reaction in the

syntheses of (-)-capnellene and (+)-xestoquinone illustrate only a few of the creative ways in which this reaction has been applied. Certainly the potential of this reaction is great, and significant advances in mechanistic understanding, catalyst development, and synthetic applications can be anticipated.

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