Review

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Pd-Catalyzed C–C, C–N, and C–O Bond-Forming Difunctionalization Reactions of Alkenes Bearing Tethered Aryl/Alkenyl Triflates

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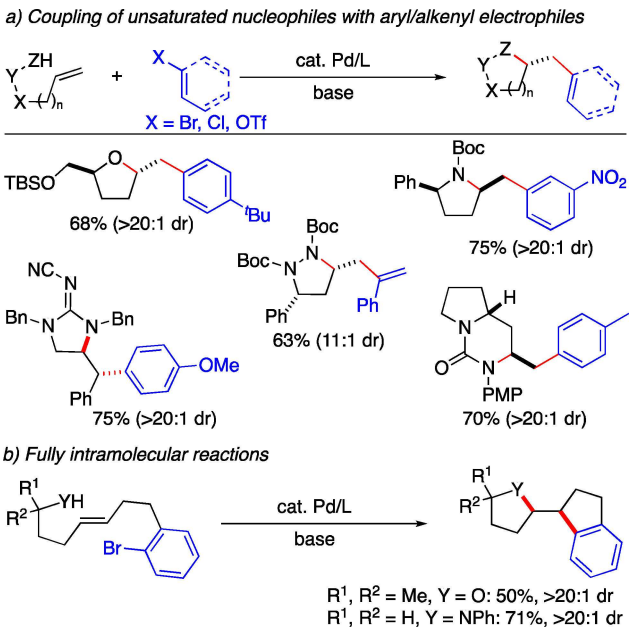
Abstract: Over the past few years our group has described a new type of alkene difunctionalization reaction in which aryl or alkenyl triflates bearing tethered alkenes are coupled with various nucleophiles to afford carbocyclic products. The products are formed in moderate to good chemical yield, with generally high levels of stereoselectivity. Our progress to date in this area, which includes reactions of amine, alcohol, enolate, and indole nucleophiles, is described in this review.

Keywords: Palladium · Alkenes · Carbocycles · Heterocycles · Cross Coupling

1. Introduction

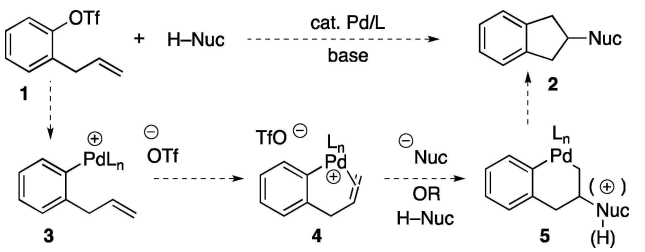
Since 2004 our group has developed and investigated a series of alkene difunctionalization reactions between aryl or alkenyl halides or triflates, and alkenes bearing tethered nucleophiles.[1,2] As shown below (Scheme 1a), these transformations affect the formation of one carbon-heteroatom bond, one carbon-carbon bond, and up to two stereocenters. The transformations afford an array of heterocyclic products, including tetrahydrofurans,[3] pyrazolidines,[4] pyrrolidines,[5] cyclic ureas[6] and cyclic guanidines,[7] in good yield and high diastereoselectivity.



Scheme 1. Synthesis of heterocycles

We have also examined fully intramolecular variants of these transformations (Scheme 1b),[8] and have demonstrated that products resulting from either *syn*- or *anti*-addition to the alkene can be selectively obtained with suitable substrates and conditions.[6e,8,9] These reactions proceed via a mechanism involving oxidative addition of the electrophile to Pd(0), followed by either *syn*- or *anti*-nucleopalladation[10] of the alkene (depending on substrate and conditions), and then C–C bond-forming reductive elimination.[1,11]

Although the transformations described above provide a straightforward means of accessing a number of different heterocyclic ring systems, in all cases the alkene was tethered to the nucleophilic component of the coupling reaction. We reasoned that by changing the arrangement of the pieces (alkene, nucleophile, and electrophile) such that the alkene was tethered to the electrophile, we could develop a new method for the synthesis of functionalized carbocycles. As shown in Scheme 2, the coupling of 2-allylphenyltriflate **1** (or related congeners) as the electrophile, combined with an external nucleophile (either anionic or neutral, depending on



Scheme 2. Planned synthesis of carbocycles

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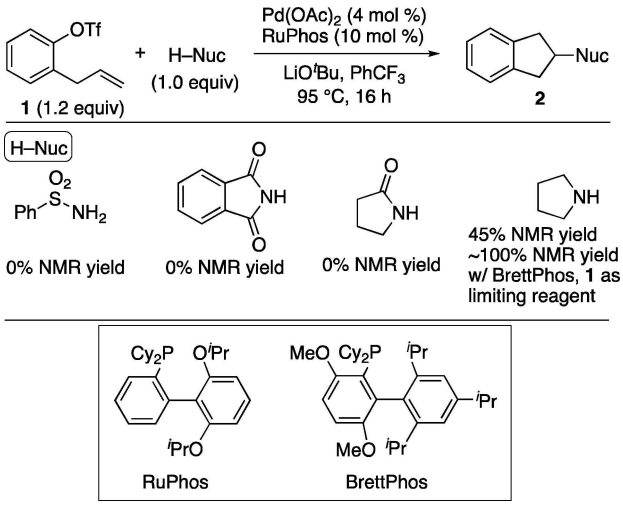
pK_a considerations; nucleophiles such as amines are likely deprotonated after the nucleopalladation step), should provide carbocyclic products **2**. Oxidative addition of the electrophile to Pd(0) would provide complex **3**, which can undergo coordination of the alkene to Pd, followed by attack of **4** by the external nucleophile to afford **5** (which may be protonated/charged, or neutral, depending on the nucleophile). Reductive elimination from **5** would then give **2**. This review summarizes our progress thus far (2015–present) on the development of this new class of alkene difunctionalization reactions.

2. Reactions of Heteroatomic Nucleophiles

2.1 Reactions of Nitrogen Nucleophiles

In preliminary studies, we sought to establish proof-of-concept results for the general transformation outlined above. As such, we elected to examine the Pd-catalyzed coupling of 2-allylphenyl triflate (**1**, prepared in one step from commercially available 2-allylphenol) with nitrogen nucleophiles (Scheme 3). Initial attempts to couple 1.0 equiv. of benzenesulfonamide, phthalimide, or pyrrolidine-2-one with 1.2 equiv. of **1** in the presence of a $Pd(OAc)_2$/RuPhos[12] catalyst system were unsuccessful. However, use of pyrrolidine as the nucleophile afforded product **2** in 45% yield. After further optimization we found that the desired product **2** was obtained in essentially quantitative yield (NMR) when BrettPhos was employed as ligand with 2-allylphenyl triflate as the limiting reagent instead of the amine nucleophile (1.0 equiv. **1**, 1.2 equiv. amine).[13]



Scheme 3. Preliminary experiments and proof-of-concept

2.1.1 Enantioselective Reactions of Aryl and Alkenyl Triflates

Once we had successfully demonstrated the desired reactivity, we elected to explore enantioselective variants of this reaction, rather than simply elucidate the scope of the racemic transformation. As such, we examined the coupling of naphthyl triflate **6** with pyrrolidine using a chiral palladium catalyst system (Scheme 4).[13] We initially examined binaphthyl-derived monodentate phosphines, and obtained promising results of up to 87 : 13 er for product **7**, but could not optimize beyond that point. After exploration of a few alternative ligand scaffolds, we discovered that phosphinooxazolines (PHOX-type ligands)[14] also provided interesting levels of asymmetric induction, and eventually found that *tert*-butyl phosphinooxazoline ligand **L6** provided the desired product **7** in 98% yield and > 99 : 1 er.[15]

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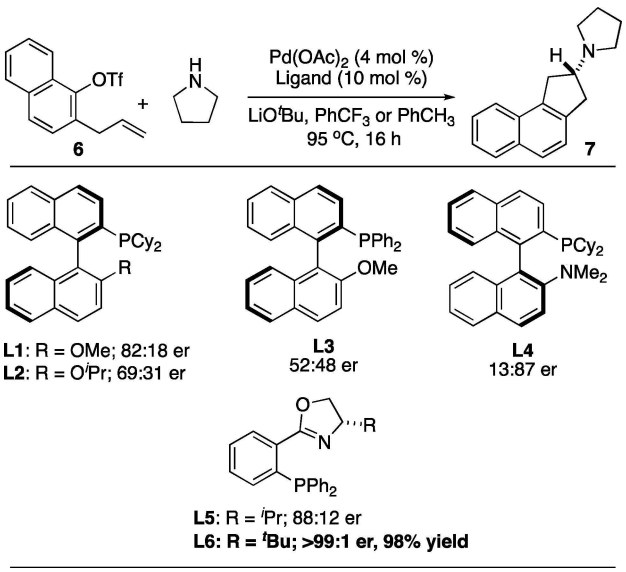


Scheme 4. Optimization of the Enantioselective Reaction

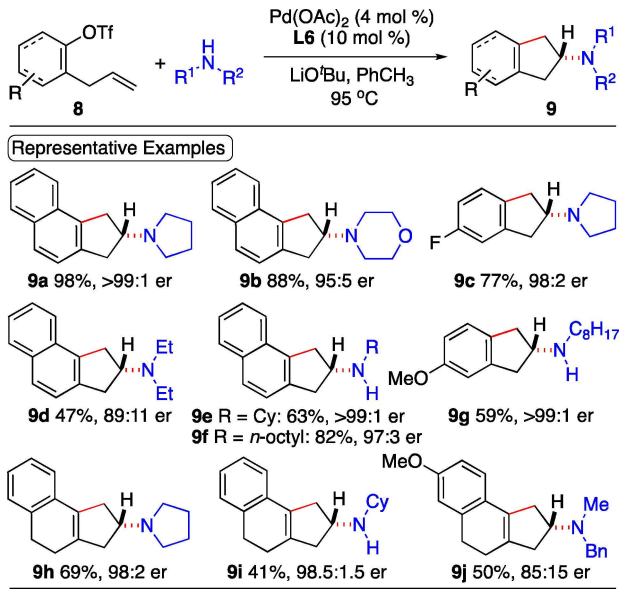
With satisfactory conditions in hand, we proceeded to explore the scope of the asymmetric alkene carboamination reactions. As shown in Scheme 5, the transformations were effective with both cyclic and acyclic secondary amines, providing good to excellent enantioselectivity. Modest yields and lower levels of asymmetric induction were obtained in the reactions of acyclic secondary amine nucleophiles (diethylamine and *N*-methylbenzylamine). Primary amine nucleophiles were also coupled in moderate to good yield and high enantioselectivity. Simple 4-substituted 2-allylphenyl triflates, along with alkenyl triflates derived from α-tetralone, proved to be suitable substrates in addition to the naphthyl triflate. Although enantioselectivities were comparable for both aryl and alkenyl triflates, the chemical yields obtained in reactions of alkenyl triflates were generally lower than those for couplings involving aryl triflates.[16]

Our current experimental evidence supports our initial mechanistic hypothesis described above in Scheme 2. In the case of amine nucleophiles, deprotonation likely occurs after, rather than before, the aminopalladation step in the catalytic cycle. Additional discussion of the mechanism and stereochemical outcomes of these general classes of reactions is provided below in Section 4.

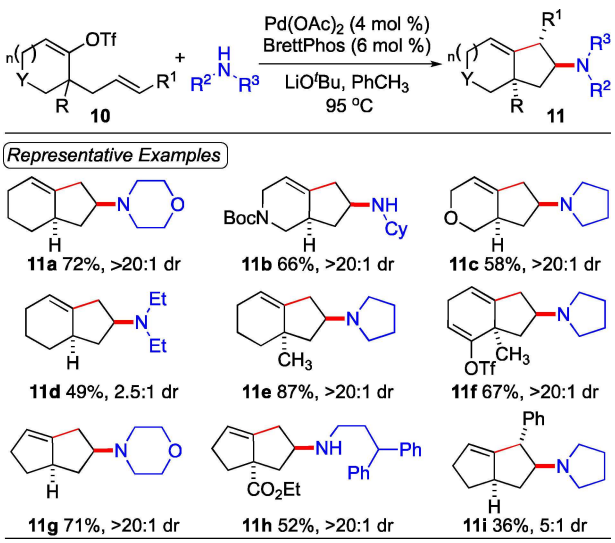
2.1.2 Diastereoselective Reactions of Alkenyl Triflates

Given the successful enantioselective reactions of alkenyl triflates described above, it seemed likely that a number of other alkenyl triflates may prove suitable substrates for these reactions. In addition, these reactions could potentially provide access to synthetically useful partially saturated carbocyclic structures. As such, we began to explore diastereoselective reactions of simple alkenyl triflates **10** generated from 2-allylcycloalkanones, which could be prepared in two steps from commercially available materials using straightforward chemistry.[16]

Fortunately, very little optimization was required. The conditions employed for the asymmetric reactions, except using BrettPhos as ligand, provided satisfactory results in these transformations (Scheme 6). The reactions were effective with a range of primary and secondary amine nucleophiles, and products **11** were generated with good to excellent levels of diastereoselectivity. The formation of both 5,5- and 6,5-fused ring systems was feasible, and the presence of an alkyl or ester substituent adjacent to the reactive allyl group was



Scheme 5. Enantioselective alkene carboamination reactions



Scheme 6. Carboamination reactions of cyclic alkenyl triflates

tolerated. In addition, a bis-alkenyl triflate derived from 1,3-cyclohexanedione was converted to aminated bicyclic alkenyl triflate product **11 f** in 67% yield and >20:1 dr.

Despite having a reasonably broad scope, the reaction was sensitive to steric effects, as the coupling of the acyclic secondary amine diethylamine proceeded in modest yield (**11 d**, 49%) and 2.5:1 dr. In addition, when a substrate bearing a 1,2-disubstituted alkene was treated with pyrrolidine, the desired product **11 i** was formed in only 36% yield and 5:1 dr.

Acyclic 1,5-dienyl triflate substrates **12** were successfully converted to exo-methylene cyclopentane derivatives **13** in moderate to good yield under our standard reaction conditions (Scheme 7).[16] However, in contrast to reactions of cyclic alkenyl triflates **10**, the stereocontrol in reactions of the acyclic substrates **12** was sensitive to ligand structure. BrettPhos provided only modest diastereoselectivity, but improved results were obtained with the more electron-rich and less sterically bulky biaryl phosphine ligands CPhos or RuPhos. With these ligands the desired products were generated in moderate to excellent diastereoselectivity (4:1 to >20:1). Discussion of the stereochemical outcome of reactions between alkenyl triflate substrates and various nucleophiles is provided below in Section 4.

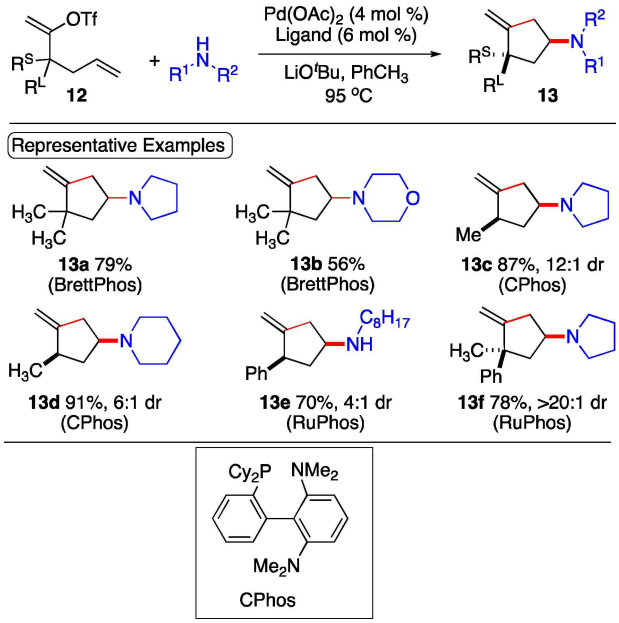
2.2 Reactions of Oxygen Nucleophiles

Due to the significance and synthetic utility of O-substituted indane derivatives,[17] we elected to explore alkene difunctionalization reactions involving oxygen nucleophiles, such as phenols or aliphatic alcohols.[18] We initially examined 2-allylphenyltriflate-derived substrates, and investigated a broader set of aryl electrophiles than in our earlier studies with amine nucleophiles. Synthesis of substrates **14** from the corresponding phenols was straightforward (three steps), and only a slight change to our previously optimized conditions was needed. With RuPhos as the ligand for palladium (in place of BrettPhos), we obtained good yields of products **15** for most substrate combinations that were examined (Scheme 8).

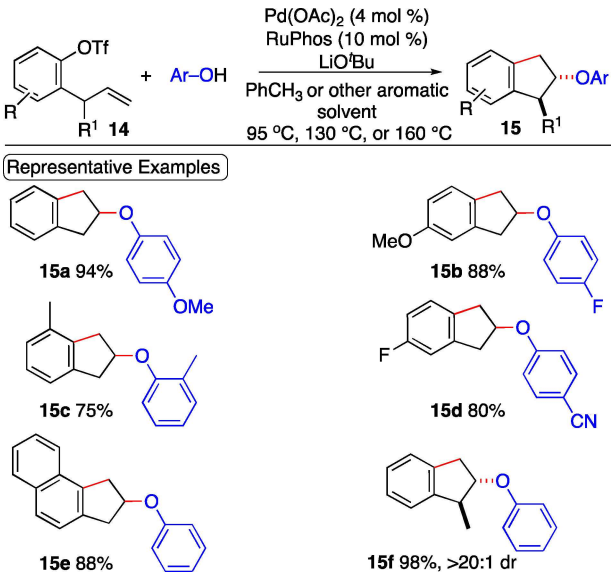
The reactions were effective with a range of phenol nucleophiles, although higher reaction temperatures of 130 °C or 160 °C were needed with electron-deficient phenols. The presence of an *ortho*-methyl group on both the aryl triflate and the phenol was tolerated (**15 c**). In addition, a substrate bearing an allylic methyl group was coupled with *p*-methoxyphenol to afford **15 f** in 98% yield and >20:1 dr. Interestingly, attempts to affect an enantioselective version of these reactions have thus far been unsuccessful. The chiral ligand **L6**, that provided excellent results with amine nucleophiles (Scheme 5), failed to promote the coupling of 2-allyl-1-naphthyltriflate with *p*-methoxyphenol. Only a trace amount of product was formed, and the reasons that **L6** does not perform well in this case remain unclear. We have yet to identify a chiral catalyst system that provides both high yield and high enantioselectivity in reactions of oxygen nucleophiles.

In addition to the aryl triflates described above, a broad series of alkenyl triflate substrates **16** proved to be suitable coupling partners with oxygen nucleophiles (Scheme 9). Both BrettPhos and RuPhos provided good results as ligands for these reactions. In some cases one of the two was slightly superior to the other, and sometimes NaO^{t}Bu was slightly superior to LiO^{t}Bu. But in many instances, either of the two ligands and bases gave comparable yields of products **17**.

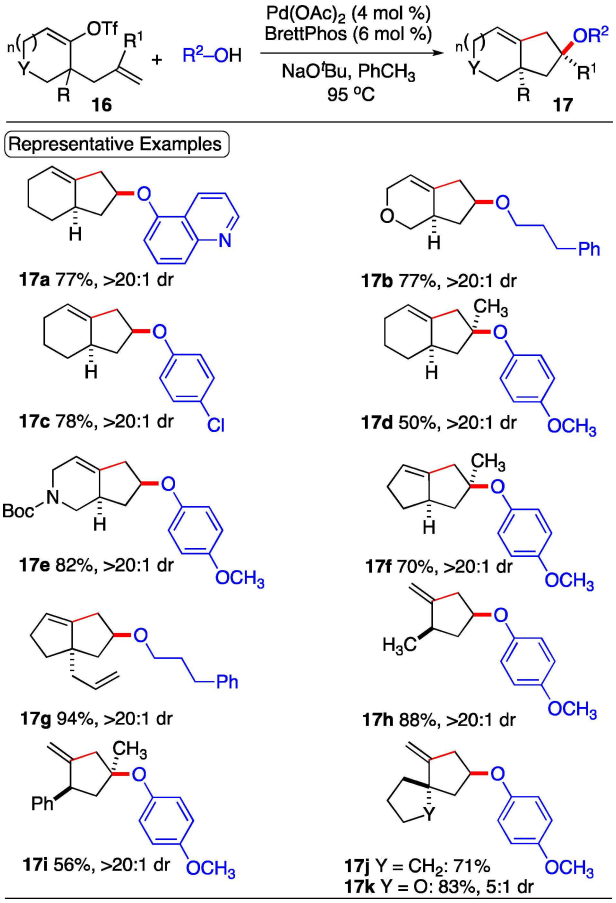
The transformations were capable of generating 6,5-fused, 5,5-fused, and 5,5-spiro ring systems in moderate to excellent yields. Diastereoselectivities were very high (>20:1) in most



Scheme 7. Carboamination reactions of acyclic alkenyl triflates



Scheme 8. Carboalkoxylation reactions of aryl triflates



Scheme 9. Carboalkoxylation reactions of alkenyl triflates

cases, and a number of different phenols and aliphatic alcohols could be employed as nucleophiles. Importantly, substitution at the internal alkene carbon of the cyclizing alkene was tolerated. Therefore, the reactions can produce tertiary alkyl-aryl ethers that would be difficult to obtain with other methods.

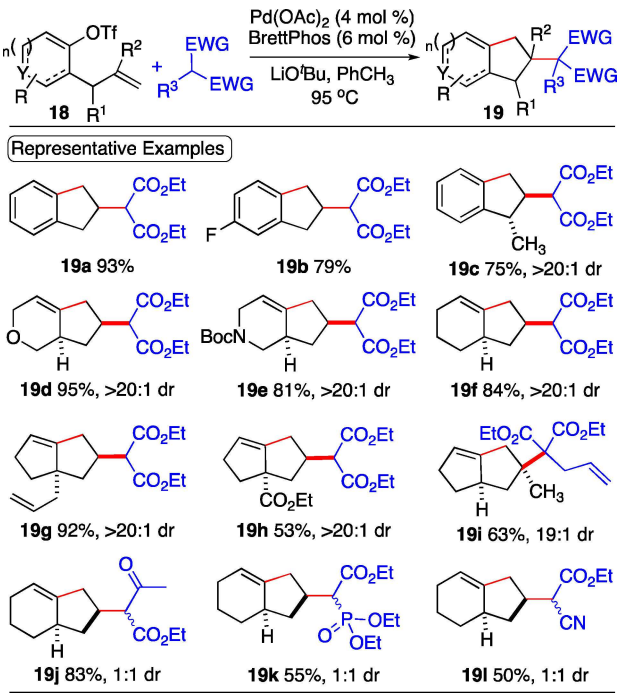
3. Reactions of Carbon Nucleophiles

3.1 Reactions of Enolates

3.1.1 Reactions of Malonates and Malonate Derivatives

Having successfully developed a new class of alkene difunctionalization reactions involving heteroatom nucleophiles, we sought to explore the feasibility and utility of related transformations of carbon nucleophiles. The use of malonates appeared to be a logical starting point, as malonate anions are good nucleophiles that have demonstrated utility in other Pd-catalyzed C–C bond-forming reactions.[19,20] As was the case with other extensions of the original coupling between pyrrolidine and 2-allylphenyltriflate, the use of malonates as nucleophiles required no optimization. The Pd/BrettPhos catalyst provided excellent results in the coupling of a range of aryl or alkenyl triflates **18** with diethyl malonate and its relatives to afford **19** (Scheme 10).[21] Diastereoselectivities were generally high, and the scope with respect to the alkenyl or aryl triflate component was comparable to that for reactions involving oxygen or nitrogen nucleophiles. Substitution adjacent to the allyl group (**19g–h**), at the allylic position (**19c**), or at the internal alkene carbon atom (**19i**), was well tolerated. Moreover, when substrates bearing 1,1-disubstituted alkenes were coupled with 2-substituted malonates, products (e.g., **19i**) bearing vicinal quaternary carbon atoms were formed in good yield and high dr. In addition to diethyl malonate and allyl diethyl malonate, we also successfully employed ethyl acetoacetate (**19j**), triethyl phosphonoacetate (**19k**), and ethyl cyanoacetate (**19l**) as nucleophiles. With some of these latter nucleophiles we needed to employ slightly modified conditions, but all provided products with high diastereoselectivity with respect to the ring fusion and nucleophile attachment stereocenters. Not surprisingly, compounds **19j–l** were obtained as 1 : 1 mixtures of diastereomers epimeric at the enolizable stereocenter.

In all of our prior studies with amine, alcohol, and phenol nucleophiles, we had demonstrated only a single example of a reaction involving a 1,2-disubstituted cyclizing alkene group (Scheme 6, **11i**), and that reaction gave a low yield and moderate dr.[16] We elected to further explore and optimize reactions of internal alkene substrates **20** using malonate nucleophiles as coupling partners. With aryl triflate derived substrates we found that the Pd/BrettPhos catalyst provided



Scheme 10. Reactions of malonates with terminal alkene substrates

modest yields that were comparable to the earlier result with pyrrolidine,[16] but products **21** were formed with excellent (> 20 : 1) diastereoselectivity (Scheme 11, **21 a**–**b**).

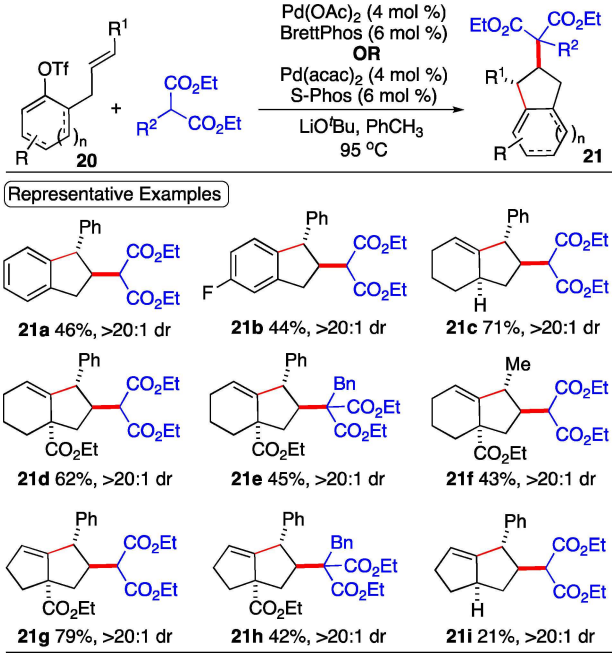
In contrast, with alkenyl triflate-derived substrates **20** that contained *trans*-1,2-disubstituted alkenes, the standard reaction conditions provided poor results. The desired products (e. g., **21 c**) were generated in < 5 % yield, and competing reduction of the triflate group was problematic. However, further experimentation showed that the use of S-Phos as ligand, with $Pd(acac)_2$ as the precatalyst, provided moderate to good yields of the desired bicyclic products with > 20 : 1 diastereoselectivity (Scheme 11). The formation of fused 5,5-membered ring systems greatly benefitted from the presence of an ester group adjacent to the allyl group of the substrate. In contrast, reactions that generated 6,5-fused bicycles provided comparable yields whether or not a substituent was present at that position. The coupling of 2-substituted malonates was possible (**21 e**, **21 h**) but gave lower yields than analogous reactions of the unsubstituted derivatives.

3.1.2 Reactions of Ketone and Ester Enolates

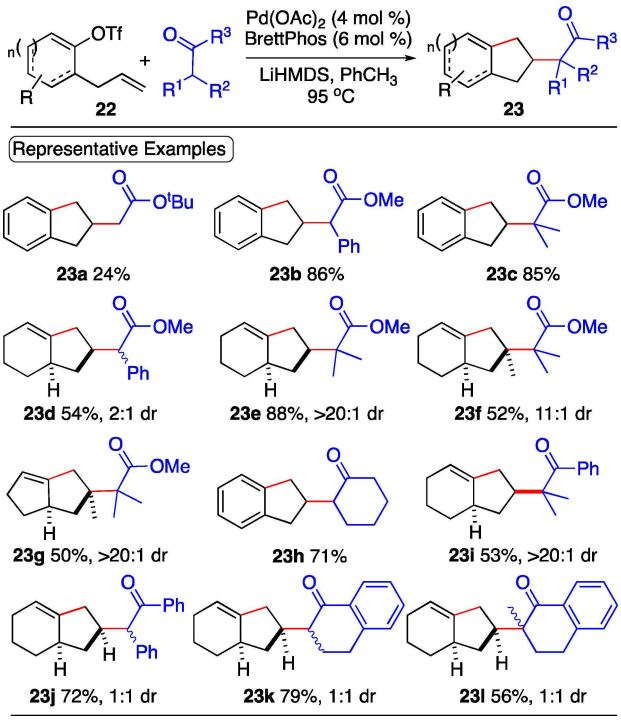
With only slight modifications to our reaction conditions (use of LiHMDS as base instead of an alkoxide), ketone and ester enolates proved to be suitable nucleophiles in alkene difunctionalization reactions of **22**.[22] Low yields of **23** were obtained with methyl ketones or acetate esters (e. g., **23 a**) due to competing Pd-catalyzed C-arylation or -alkenylation of the starting material.[19a] However, products **23** were generated in good to excellent yields with mono- or di-substituted ketones or esters. The products of these reactions were obtained in high diastereoselectivity except for those that contained an α-carbonyl stereocenter (**23 d**, **23 j**–**k**). In those cases, 1 : 1 mixtures of diastereomers were obtained that were epimeric at the stereocenter adjacent to the carbonyl. In addition to the obvious problem of base-mediated epimerization for products bearing an enolizable stereocenter, there appears to be poor relative face selectivity when the enolate engages the alkene in the intermediate organopalladium complex (Scheme 12, **4**), as the reaction of α-methyl tetralone provided **23 l** in 1 : 1 dr. Interestingly, cyclohexanone underwent selective mono-alkylation in good yield (**23 h**). As was the case with malonate nucleophiles, the formation of bonds between contiguous quaternary carbon atoms was feasible in reactions that employed ester enolates (**23 f**–**g**). However, in contrast to transformations involving malonate nucleophiles, efforts to employ substrates bearing 1,2-disubstituted cyclizing alkenes have been unsuccessful with ketone and ester enolates.

3.2 Reactions of Indoles

In order to further explore the scope and limitations of this class of alkene difunctionalization reactions, we elected to study reactions of heteroaromatic compounds.[23] We were curious as to whether or not weak carbon nucleophiles, such as indoles, would participate in these reactions, and if so, whether they would react as carbon- or nitrogen-nucleophiles.



Scheme 11. Reactions of malonates with internal alkene substrates



Scheme 12. Reactions of ketone and ester enolates

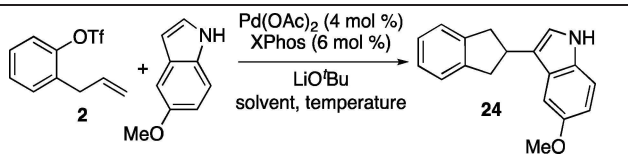
During preliminary optimization studies, we found that reaction conditions comparable to those used with other nucleophiles described above did lead to the conversion of **2** to the desired product **24** (Table 1). However, the results were highly irreproducible, and chemical yields varied widely from run-to-run when conducted in toluene at a 0.1 M reaction concentration. We reasoned that increasing the reaction concentration, or increasing the equivalents of indole added, may improve yields given the relatively poor nucleophilicity of indoles. But, further increasing the reaction concentration up to 1 M did not provide significantly better results, and separation of the excess indole from the product was difficult.

Ultimately, a key observation led to a solution of the reproducibility problem. In order to try to conduct as many reactions as possible in as short time period, the transformations were conducted in screw-capped vials in a metal heating block. Not every vial cap had a perfect seal, and in some instances the reaction solvent evaporated during the overnight run. Interestingly, the best results were obtained in the reactions where the solvent had evaporated.

We reasoned that the extremely high concentration of indole present in the solvent-evaporated reaction mixtures was probably facilitating the transformations of these weak nucleophiles, and subsequently examined conducting reactions without solvent. Unfortunately, omitting solvent entirely also did not provide satisfactory reproducible yields.

It seemed that the lack of success with "neat" reaction conditions may be due to inefficient catalyst ligation/activation, since the only liquid present in the reaction mixture was the aryl triflate **2**. Based on this hypothesis, we devised a new reaction protocol, in which the reactions were set up using benzene as the solvent.[24] The reactions were conducted in round-bottom flasks equipped with a short-path distillation head, and after reagents were mixed, the reaction flask was heated to 100 °C and the benzene solvent was removed via distillation. The reaction temperature was then decreased slightly to 95 °C, and the reactions were allowed to stir for 3 h at this temperature in little or no solvent. These conditions proved to give satisfactory and reproducible yields.

Table 1. Experimental Protocol.



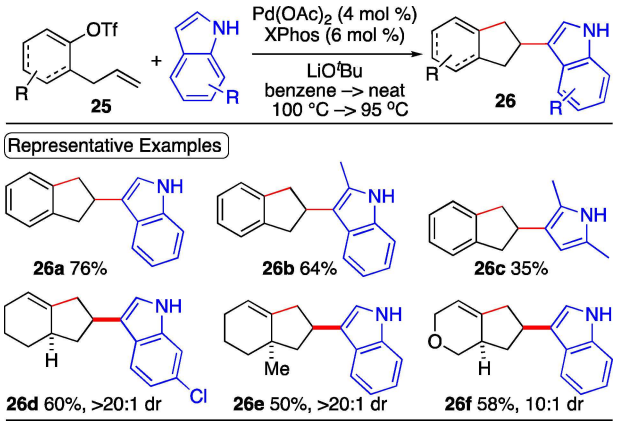
solvent	temperature	result
Toluene (0.1 M to 1 M)	95 °C	up to 62% yield, but irreproducible
none	95 °C	variable, irreproducible yields
Benzene (1 M –> ~neat)	100 °C to 95 °C (solvent removed via distillation during initial reaction)	**66% yield, reproducible**

As shown in Scheme 13, several different substituted indoles were suitable substrates. In all cases the indole alkylation occurred at C3, and competing N-alkylation was not observed. The presence of the indole N–H group was essential, as N-alkyl indoles did not participate in the reaction. Unfortunately, efforts to extend this method to other heteroaromatic systems have thus far been unsuccessful. No reaction was observed with benzofuran or benzothiophene. The coupling of 2,5-dimethyl pyrrole did afford the desired product, but yields were modest due to oxidation of the electron-rich pyrrole product during the course of purification.

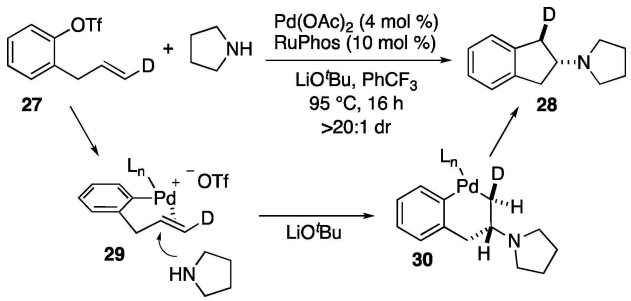
Both aryl and alkenyl triflates **25** were effective coupling partners, and products **26** were formed with good to excellent diastereoselectivity. However, the transformations were quite sensitive to steric properties of the substrate. Aryl triflates bearing substituted alkenes failed to react, and a substrate with a methyl group at the allylic position was transformed in low yield.

4. Mechanism and Stereochemistry

Our initial mechanistic hypothesis (Scheme 2) suggested that the products of these reactions should result from net addition of the nucleophile and the aryl (or alkenyl) group to the cyclizing double bond. In order to probe this hypothesis, we examined the stereochemical outcome of the reaction between pyrrolidine and deuterated alkene substrate **27**.[13] As shown in Scheme 14, this reaction afforded *trans*-disubstituted product **28** as a single diastereomer (>20:1 dr). This result is consistent with our original hypothesis, involving oxidative addition to afford **29**, *anti*-aminopalladation of the alkene to give **30**, and then reductive elimination to provide the product **28**. The *anti*-nucleopalladation pathway also appears operative in reactions involving soft, anionic nucleophiles as well. Coupling reactions between *trans*-1,2-disubstituted alkene substrates and malonate nucleophiles also afforded products with a *trans* relationship between the *E*-alkenyl substituent and the nucleophile (Scheme 11, **21 a**–**i**).



Scheme 13. Reactions of indole nucleophiles

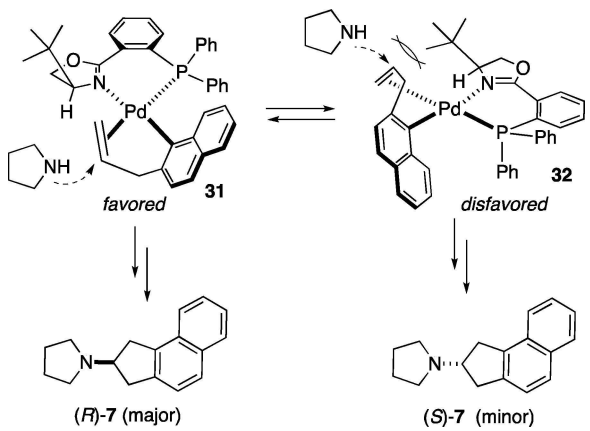


Scheme 14. Stereochemistry of alkene addition

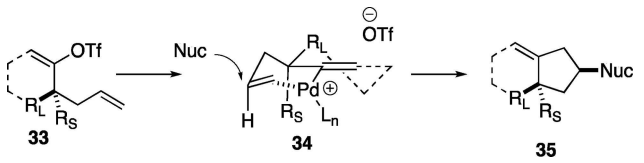
Our working model to explain both absolute and relative stereochemistry in these transformations is based on the mechanistic hypothesis derived above. We believe that the alkene hetero- or carbo-palladation step is likely the stereo-determining step of these reactions, but this step may be reversible depending on the nucleophile.[25] Our current stereochemical model does provide explanations for the origin of the major enantiomer or diastereomer in these transformations, but does not account for the influence of small changes to structure (sterics or electronics) on stereoselectivity.

Our working hypothesis for the origin of enantioselectivity in the Pd/*t*-butyl-phosphinooxazoline catalyzed reactions is based on a model originally proposed by Guiry for asymmetric Heck reactions.[26] As shown in Scheme 15,[13] following oxidative addition of the substrate, the alkene can bind to the metal such that the less-substituted carbon is relatively close to the bulky *tert*-butyl group (**31**), or with the more substituted and more hindered carbon of the alkene closer to the *tert*-butyl group (**32**, via rotation around the Pd–C_{Ar} bond axis). Reaction through the apparently less-sterically hindered and favored complex **31** leads to the observed major stereoisomer (*R*)-**7**.

We believe the relative stereochemistry in transformations of alkenyl triflate substrates is largely controlled by reaction through an organized, chair-like, transition state during the alkene nucleopalladation step of the catalytic cycle. As shown



Scheme 15. Model for enantioselectivity



Scheme 16. Model for diastereoselectivity

in Scheme 16, binding of the alkene through transition state **34**, in which the smaller group (R_S) is oriented in an axial position, would afford products with the observed relative stereochemistry between the nucleophile and the smaller substituent adjacent to the cyclizing allyl group. We cannot currently explain the influence of biaryl phosphine structure on stereocontrol that was observed in reactions of acyclic alkenyl triflates (Scheme 7), although it is possible that larger phosphines (e.g., BrettPhos) may result in reaction through pseudoaxial orientation of the cyclizing alkene.

5. Summary and Outlook

In conclusion, we have developed a new class of alkene difunctionalization reactions between aryl or alkenyl triflates bearing tethered alkenes, and nucleophiles such as amines, alcohols, enolates, and indoles. The transformations generate two bonds, 1–2 stereocenters, and proceed in good yields and high diastereoselectivities for most cases. However, many important challenges remain unsolved, including the development of enantioselective variants of these reactions that have broad scope and generality, and controlling stereochemistry in reactions of prochiral nucleophiles (e.g., cyclohexanone). Many useful classes of nucleophiles have not yet been explored, and fully intermolecular reactions between an alkene, an aryl/alkenyl halide/triflate electrophile, and a nucleophile have not been developed. These problems will be examined and addressed during future studies.

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