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Consecutive Carbon-Carbon Bond Formation via the π-Allylpalladium Variant of the Heck Reaction

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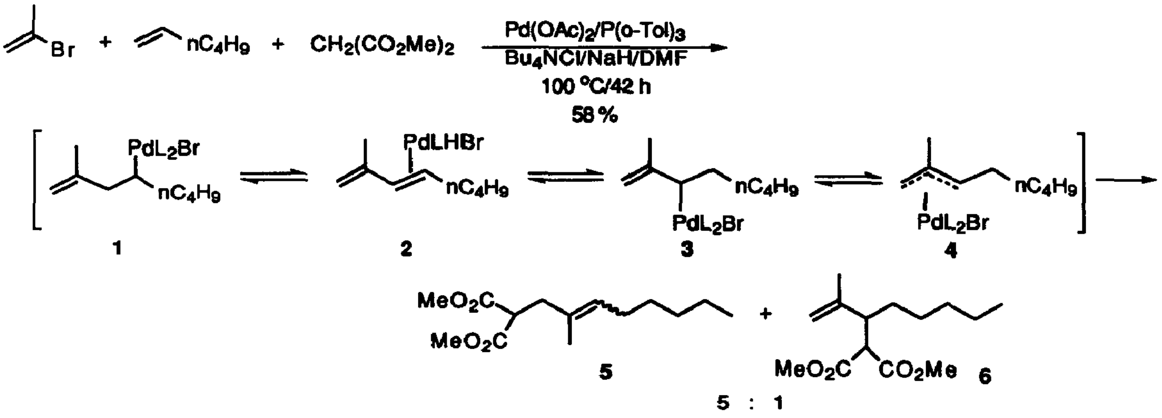
Abstract: Two C-C bonds are readily formed by nucleophilic addition of stabilized carbanions to the π-allylpalladium intermediate regioselectively produced by the Heck reaction of a vinyl bromide and an unactivated olefin. An intramolecular version of this condensation gives functionalized carbobicyclic compounds as products.

The Heck reaction is a powerful C-C bond-forming method.[1] Both inter- and intramolecular variations of this palladium-catalyzed coupling of an aryl or vinyl halide with an olefin have found widespread use in synthesis.[2] The reaction of a vinyl halide with an unactivated olefin can produce a stable π-allylpalladium species which sequesters the palladium and thus ends the catalytic cycle. The inclusion of a secondary amine in the reaction mixture results in the formation of an allylic amine and the regeneration of the metal catalyst.[3] We considered combining the vinyl halide, olefin, and a nucleophile into one substrate thus allowing this condensation to be achieved intramolecularly. We have in fact shown that the Heck reaction can be used to generate π-allylpalladium species regiospecifically which are then trapped internally by sulfonamide nucleophiles to form a variety of nitrogen heterocycles.[4]

As an extension of our earlier work, we have now investigated the addition of carbon nucleophiles to π-allylpalladium species formed regiospecifically via the Heck reaction.[5] Our initial studies focused on a three component intermolecular reaction. Combining 2-bromo-1-propene with 1-hexene and dimethyl malonate using sodium hydride as the base under the conditions shown[6,7] produced a 5:1 mixture of olefinic diesters **5** (a single isomer of undetermined configuration) and **6** in 58% combined yield (**Scheme I**).[8]

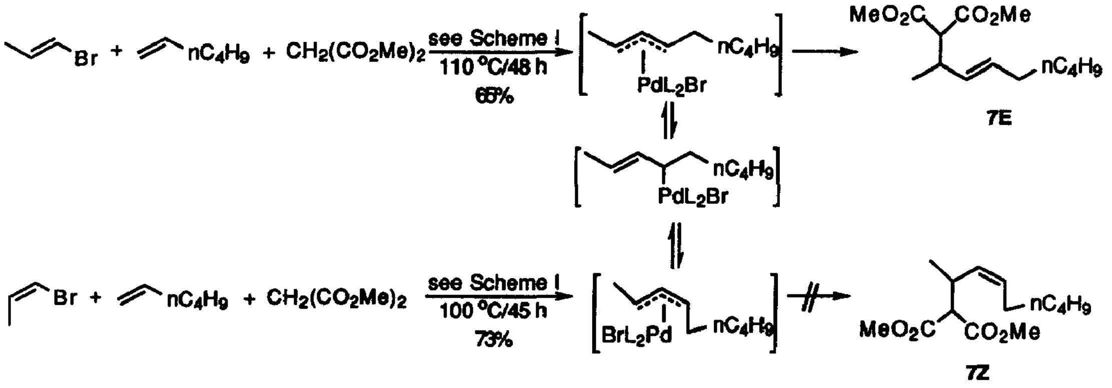
Scheme I



The proposed mechanism of this tandem C-C bond-forming reaction is shown in **Scheme I**. 2-Bromo-1-propene first adds to 1-hexene to produce σ-palladium species **1**, which β-hydride eliminates, yielding η^2-complex **2**. Regiospecific readdition of PdH to the π bond to which the metal is complexed gives the σ-allylpalladium compound **3** which then rearranges to the π-allylpalladium complex **4**. The major product **5** is the result of nucleophilic addition of sodium dimethyl malonate to the terminal end of **4**, whereas **6** arises from addition to the internal end. This product distribution is well established in additions of stabilized carbanions to related π-allylpalladium species formed by alternative methods.[5b,9]

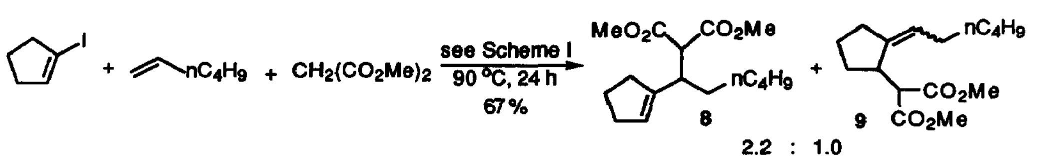
To investigate the effect of the stereochemistry of the vinyl bromide double bond in this reaction, Z- and E-1-bromo-1-propene were subjected to the reaction conditions (**Scheme II**). The reaction of E-1-bromo-1-propene produced compound **7E** as the sole product in 65% yield.

Scheme II



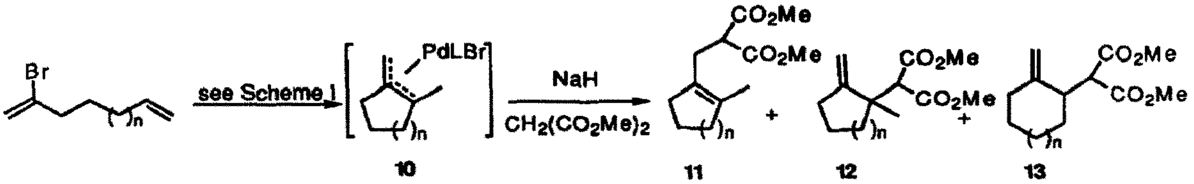
The reaction of Z-1-bromo-1-propene also formed compound **7E** as the only product in 73% yield when subjected to the reaction conditions. The transformation of the Z olefin to an E product probably occurred through the established π-σ-π isomerization of π-allylpalladium species (**Scheme II**).[10]

Cyclic vinyl halides can also function effectively as substrates in this condensation. When 1-iodo-1-cyclopentene was subjected to the reaction conditions, a mixture of regioisomeric products **8** and **9** were formed in a 2.2:1.0 ratio in 67% combined yield (**eq 1**).[8,11]



(1)

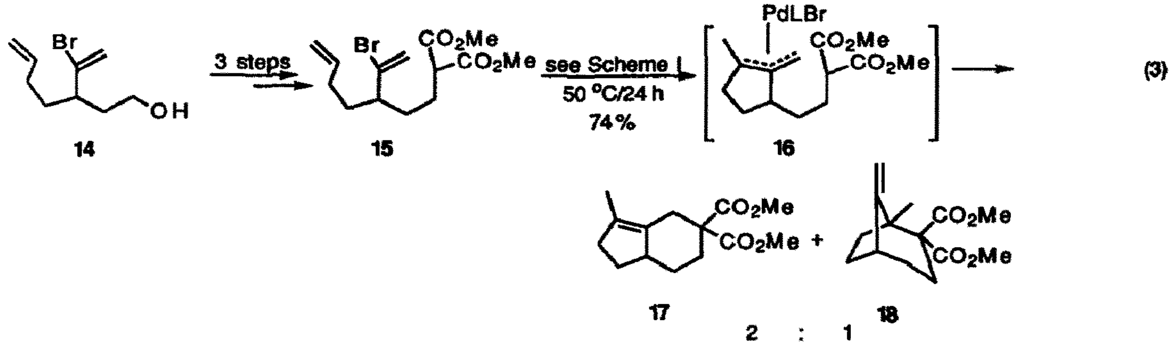
An intramolecular Heck reaction of a vinyl halide/olefin followed by trapping the resultant π-allylpalladium species with an external nucleophile was also successful.[12] The Heck reaction of 2-bromo-1,6-heptadiene produces the π-allylpalladium species **10a** through a 5-exo ring closure,[13] which is trapped by sodium dimethyl malonate to produce cyclopentyl derivatives **11a** and **12a** (**eq 2**, n=1). Again the major product **11a** was formed from addition of the nucleophile to the less substituted and, in this case, exocyclic terminus of the π-allylpalladium complex. A small amount of cyclohexyl derivative **13a** was also seen, arising from initial 6-endo Heck cyclization and nucleophilic addition to the less substituted end of the resulting π-allylpalladium complex.[4] The products were formed in 80% combined yield with **11a**, **12a**, and **13a** being formed in a ratio of 4.0:1.5:1.[14]



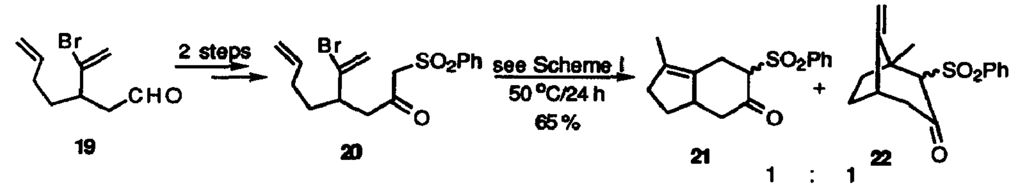
		11		12		13	
a) n=1	90 °C/26 h/80 %	4.0	:	1.5	:	1.0	(2)
b) n=2	100 °C/43 h/63 %	0	:	1.0	:	0	

The homologous substrate, 2-bromo-1,7-octadiene,[13] formed only one product when subjected to similar reaction conditions (eq 2, n=2). The Heck cyclization proceeds exclusively in a 6-exo fashion to produce the π-allylpalladium species **10b**, which is trapped by sodium dimethyl malonate addition to the endocyclic, more substituted terminus to give **12b** in 63% yield. This particular π-allylpalladium species has been prepared earlier by other means. The observed "anomalous" regiochemistry of nucleophilic attack on **10b** has been previously attributed to disfavorable steric interactions between the axial protons on the ring and the bulky o-tolylphosphine ligands on the palladium due to the rigid conformation of the cyclohexane ring causing the palladium to be more closely complexed to the exo portion of the allyl moiety, thus freeing the endocyclic position for nucleophilic attack.[9,15]

To effect this condensation totally intramolecularly, substrates were synthesized which contain the vinyl halide, olefin, and nucleophile. The dimethyl malonate derivative **15**, prepared in three steps from the known alcohol **14**,[4] was subjected to the reaction conditions shown to produce a 2:1 mixture of bicyclic compounds **17** and **18** in 74% yield (eq 3). The reaction probably proceeds through the π-allylpalladium species **16**, which is attacked by the internal nucleophile at both termini to give the fused and bridged bicyclic compounds. The major product **16** is formed from internal nucleophilic attack on the less substituted end of the π-allylpalladium species.



Similarly, the β-keto sulfone **20**, prepared in two steps from the known aldehyde **19**,[4] was cyclized under the conditions shown to produce the fused product **21** and bridged product **22** in a 1:1 ratio and 65% combined yield (eq 4). We have no explanation at this time for the lack of regioselectivity of the nucleophilic attack onto the presumed π-allylpalladium complex.



(4)

The tandem Heck reaction-nucleophilic addition to π-allylpalladium species has been demonstrated to be a useful method for the consecutive formation of two C-C bonds and, when performed intramolecularly, the rapid construction of functionalized carbobicyclic systems. Application of this condensation to the synthesis of some natural products is currently in progress.

Acknowledgement. We are grateful to the National Science Foundation for financial support on grant CHE-92-02848.

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6. General reaction procedure: a mixture of 2.0 eq of Bu_4NCl[7] and 2.0 eq of NaH was rapidly stirred in DMF in a resealable tube under argon as the nucleophile (2.0 eq) was added dropwise. When gas evolution ceased, 0.05 eq of $Pd(OAc)_2$ and 0.10 eq of $P(o\text{-}Tol)_3$ were added, followed by a solution of 1.0 eq of alkene and 1.0-2.0 eq of vinyl halide in DMF. The mixture was degassed and the reaction vessel was sealed under reduced pressure. The reaction was heated at the temperature and for the time shown in the equations. After cooling the reaction mixture and filtering it through a short column of flash silica gel with 50% ether/hexanes, the products were isolated by flash chromatography. All compounds showed satisfactory spectral data.
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8. The product ratio was determined by integration of the vinyl proton peaks in the ^1H NMR.
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