Endo-Selective Cyclization Pathways in the Intramolecular Heck Reaction

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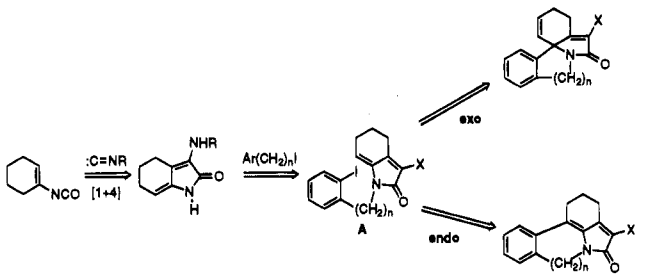
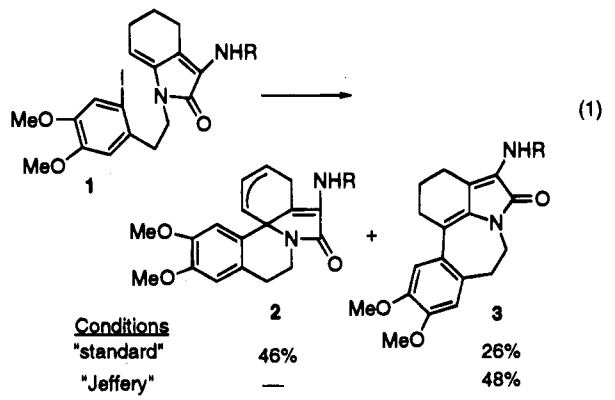
The intramolecular version of the palladium-catalyzed arylation of alkenes has emerged as a powerful method for the construction of complex organic molecules.[1] An overwhelming preference for the exo mode of cyclization has been noted in most cases,[2] and even when products ostensibly derived from an endo process have been observed, evidence supporting an initial exo addition followed by rearrangement has been presented.[3] A few authentic examples of transformations following the much rarer endo reaction channel have surfaced; however, these have usually appeared in situations where the exo pathway has been precluded in one fashion or another.[2a,4] Clearly, the synthetic utility of the intramolecular Heck process would be enhanced if conditions permitting selective endo cyclization could be identified. As a partial solution to this problem, we report on Heck reaction conditions that afford products with high endo selectivity in a range of substrates of general structure **A**. The ability to effect selective cyclizations on these species could permit efficient access to a range of alkaloid ring systems from essentially a common intermediate. For example, endo cyclization of **A** ($n = 1$) would lead to the lycorane (Amaryllidaceae) ring system,[5] while the exo pathway would provide the erythrina ($n = 2$) or homoerythrina ($n = 3$) skeletons, respectively.[6]

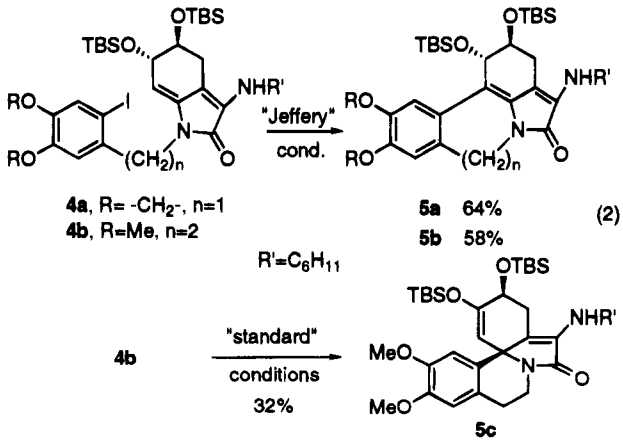


Substrates exhibiting various tether lengths ($n = 1-3$) were readily prepared using the recently reported [1 + 4] vinyl isocyanate−alkyl isocyanide cycloaddition protocol[7] followed by selective N-alkylation with appropriate aryl iodide species.[8] Several palladium-catalyzed transformations were then examined to effect selective cyclization to the target tetracyclic products. Treatment of hydroindolinone **1** (R = *p*-MeOC$_6$H$_4$) under "standard" Heck conditions ($Pd(OAc)_2$ (10 mol %), (*o*-tol)$_3$P (20 mol %), Et_3N (2 equiv), MeCN/H_2O (10:1), 80 °C)[9] afforded a mixture of the expected exo product **2**[10] accompanied by a lesser amount of the unanticipated endo-derived product **3**.[10] The production of the latter material, even in minor quantities, was surprising in light of the trends delineated above. Remarkably, exposure of the same enamide to the Jeffery palladium catalyst system[11] ($Pd(OAc)_2$ (10 mol %), *n*-Bu_4NCl (2 equiv), KOAc (5.5 equiv), DMF (0.2 M), 100 °C) provided *only* the product derived from the endo cyclization pathway. These observations suggest that an opportunity exists for effecting either exo or endo cyclization selectively on the same substrate by proper choice of reaction conditions.



(1)

The endo selective cyclization pathway proved to be easily extended to more highly functionalized systems as evidenced by the relatively efficient conversion of **4a,b**[10] into the corresponding tetracyclic products **5a,b**[10,12] depicted in eq 2. In contrast, exposure of **4b** to "standard" reaction conditions afforded only the product of an exocyclic pathway.



(2)

† Author to whom inquiries concerning the X-ray crystallographic determinations should be directed.

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(10) This compound displayed spectral (^{1}H NMR, ^{13}C NMR, IR, MS) and analytical (combustion analysis and/or HRMS) data in complete accord with the assigned structure.

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(12) The structure of this material was confirmed by single-crystal X-ray analysis. Details will be reported at a later time.

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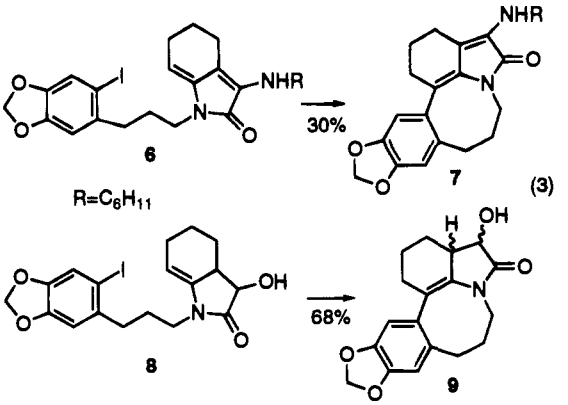
An appealing rationale for the unusual regioselectivity exhibited by the reactions employing the Jeffery conditions would implicate the involvement of a relatively small metal coordination sphere that could be well accommodated at the more substituted alkene site during migratory insertion.

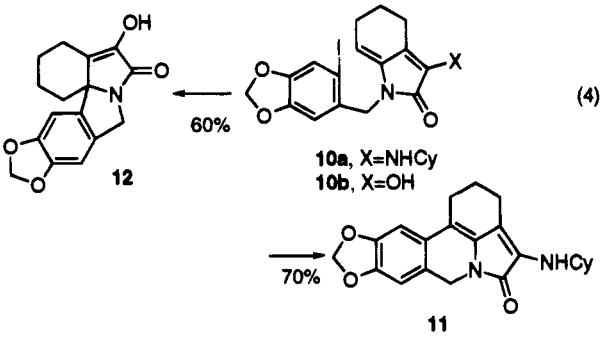
Additional insight into the factors controlling these reactions may be gleaned from the results in eq 3. In this instance, compound **6**[10] afforded the 8-endo product **7**[10] in only 30% yield with the Jeffery conditions whereas the functionally isolated enamide **8**[10] provided the corresponding eight-membered-ring product **9**[10] as a mixture of diastereomers in 68% yield under identical conditions. These observations are suggestive of a role for the enamide function in dictating regioselectivity, possibly through electronic effects. The regiochemical exclusivity of the transformation of **8** to **9**, however, appears to be inconsistent with some recent mechanistic arguments, which predict either mixtures of regioisomers or exclusive formation of the alternate isomer in Heck reactions with enamides.[13] These arguments were formulated in the context of intermolecular processes and, consequently, may be outweighted by ring size constraints in the current examples. It is also noteworthy that 1,3-dienes are known to undergo Heck reaction exclusively at a terminal position under either "standard" [14a,b] or "Jeffery" conditions.[14c] However, substrates **1** (eq 1) and **4b** (eq 2) afford products derived primarily or exclusively from an exocyclic mode of addition under "standard" Heck conditions, while only endo-addition products are isolated from the same starting materials using the Jeffery catalyst system (eqs 1 and 2). Since the exocyclic pathway in these substrates can be viewed as an addition to an internal position of a diene, it appears that the presence of this function is not a controlling factor in these reactions.

With regard to the original objective of this study, conditions have indeed been identified that permit the efficient execution of either an exo- or an endo-selective ring-forming process by minor substrate modification coupled with a proper choice of catalyst system. Thus, employing Jeffery conditions on enamine **10a**[10] afforded the expected endo product **11**[10] in good yield, while the enol derivative **10b**[10] afforded exclusively **12**[10,12] on exposure to standard Heck conditions. It is presumed that the latter reaction proceeds via the conjugated enone tautomer of



(3)

10b and initially yields a palladium enolate[15] upon cyclization that subsequently collapses to the observed product.



(4)

Further work is planned to extend the observations made to date with these transformations and to apply the methodology to the synthesis of several alkaloid targets.

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Supporting Information Available: Experimental procedures and complete spectroscopic data for compounds **2**, **3**, **5a–c**, **7**, **9**, **11**, and **12** (7 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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