SYNTHESIS OF HETEROCYCLES USING THE INTRAMOLECULAR HECK REACTION INVOLVING A 'FORMAL' ANTI-ELIMINATION PROCESS

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Abstract - This review summarizes the synthetic studies of a variety of heterocycles using the intramolecular Heck reaction which involves a formal *anti*-elimination of HPdX.

Introduction

A palladium(0)-catalyzed coupling reaction of an aryl or a vinyl halide with an alkene, called the Heck reaction,[1] has established itself as a powerful and efficient method for the construction of heterocycles[2] as well as carbocycles.

A generally accepted mechanism of the Heck reaction can be summarized in the following five steps; (i) oxidative addition of an aryl halide to a Pd(0) species to form an ArPdX intermediate, (ii) formation of a π-complex from the arylpalladium intermediate with an alkene, (iii) decomposition of the π-complex with the carbon-carbon bond and carbon-Pd bond formation in a *syn*-addition manner to produce a σ-complex, (iv) β-elimination of hydridopalladium halide (HPdX) if a β-H having *cis*-stereochemical relationship to the PdX species is present, and (v) reductive elimination of HX from HPdX into Pd(0) by a base to start another catalytic cycle (Figure 1).

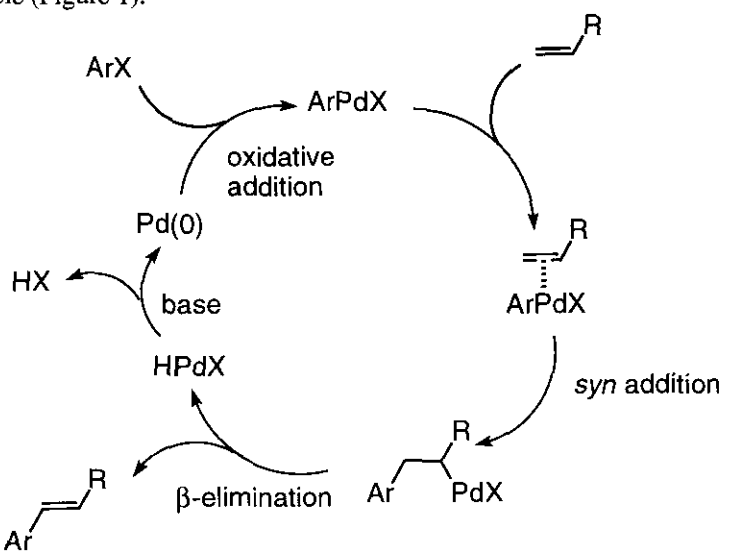
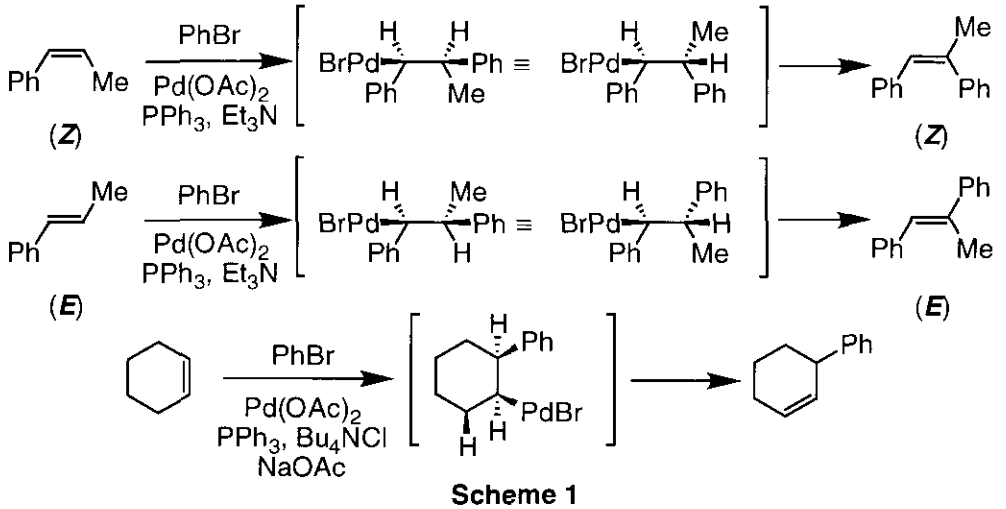


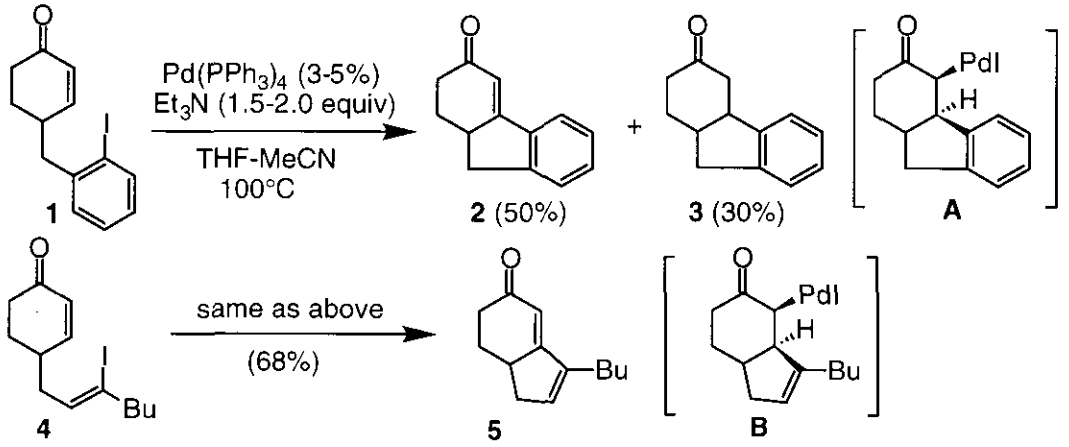
Figure 1

The outcome of the Heck reaction is consistent with a *syn*-addition of the Ar-PdL_n to the alkene, followed by a *syn*-elimination of HPdX to reform the alkene linkage. For example, the Heck reaction of bromobenzene with (*Z*)-1-phenylpropene produced a 73% yield of (*Z*)-1,2-diphenylpropene, while the (*E*)-congener gave a 79% yield of the (*E*)-1,2-diphenylpropene.[3] Consistent with these results is the fact that the reaction of bromobenzene with cyclohexene gives largely 3-phenylcyclohexene (Scheme 1).[4]



Scheme 1

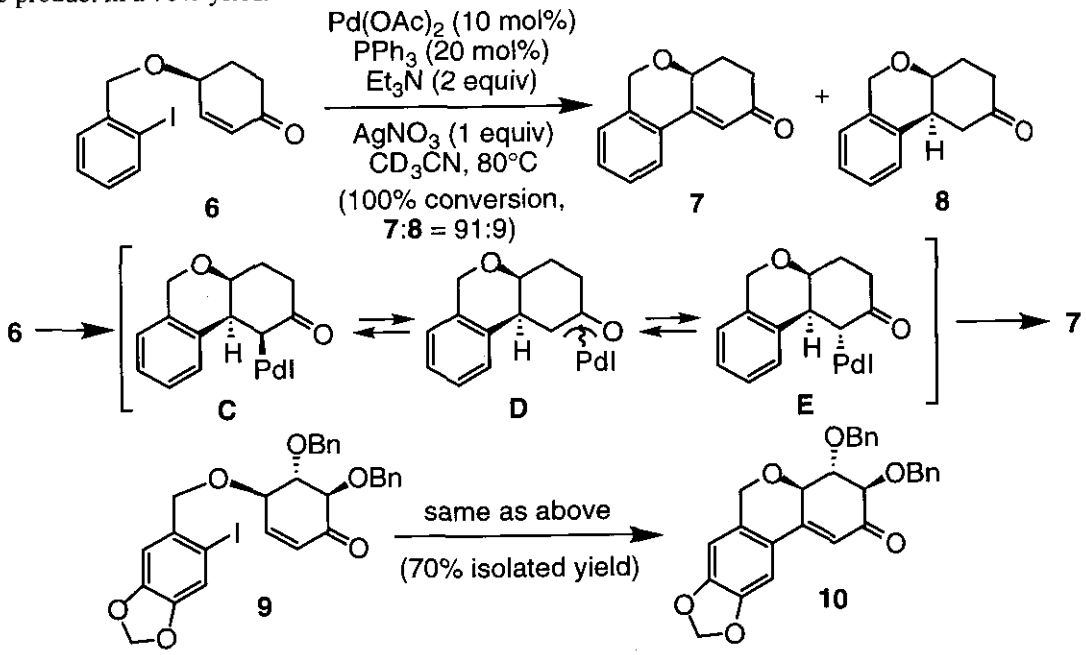
Recently, a number of examples have been reported which do not follow this *syn*-addition/*syn*-elimination mechanism. A typical example is an annulation of the 2-cyclohexenone derivatives (**1** and **4**) using the intramolecular Heck reaction (Scheme 2).[5] Under the Pd-catalyzed cyclization conditions, the aryl iodide (**1**) was converted into the enone (**2**) in a 50% yield along with a 30% of the saturated ketone (**3**), whereas a similar reaction of the vinyl iodide (**4**) gave only the enone (**5**) in a 68% yield. The formation of **2** and **5** involves a formal *anti*-elimination of HPdI from possible intermediates (**A**) and (**B**), respectively. This review summarizes the synthetic studies of a variety of heterocycles using the intramolecular Heck reaction which involves a formal *anti*-elimination of HPdX.



Scheme 2

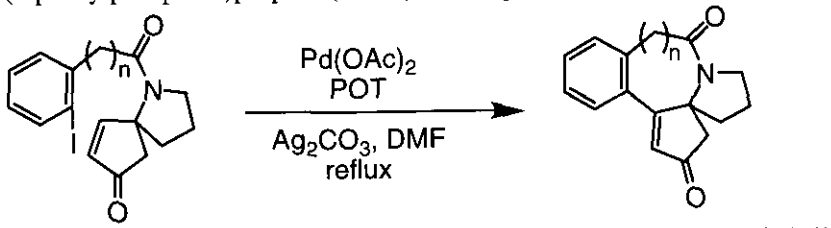
1. The Intramolecular Heck Reaction with α,β-Unsaturated Carbonyl Systems

Branchaud and coworkers reported that the Pd-catalyzed reaction of **6** gave the cyclic ethers (**7**) and (**8**) as a 91:9 mixture under the conditions [$Pd(OAc)_2$, PPh_3, Et_3N, and $AgNO_3$ in CD_3CN at 80 °C] (Scheme 3).[6] One possible explanation for the formation of **7** would involve an apparent *anti*-elimination of HPdI from the initially formed σ-palladium complex (**C**), which should be long-lived enough to eventually epimerize to an intermediate (**E**) possessing *syn*-β-H through an oxo-β-allylpalladium intermediate (**D**).[7] The normal *syn*-elimination then occurs to produce **7**. A similar reaction of **9** gave the enone (**10**) as a sole product in a 70% yield.



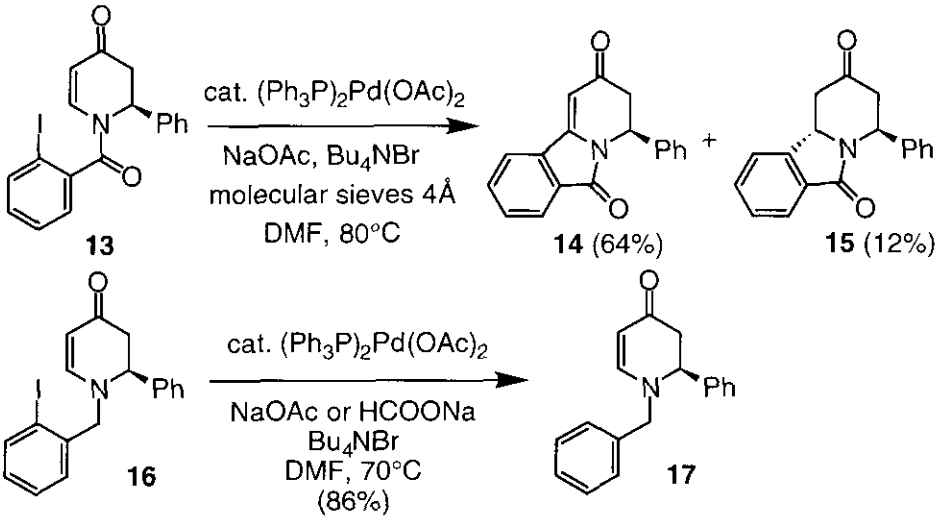
Scheme 3

We also reported an approach to the cephalotaxine skeleton using the intramolecular Heck reaction of the compounds (**11a,b**) (Scheme 4).[8] When **11a,b** were subjected to the Heck reaction conditions [$Pd(OAc)_2$, tris(*o*-methylphenyl)phosphine (*POT*), and Ag_2CO_3 in DMF], the target pentacyclic compounds (**12a,b**) were obtained in 66 and 35% yields, respectively. The yield of **12b** increased to 51% when 1,3-(diphenylphosphino)propane (DPPP) and Bu_3P were used as ligands.

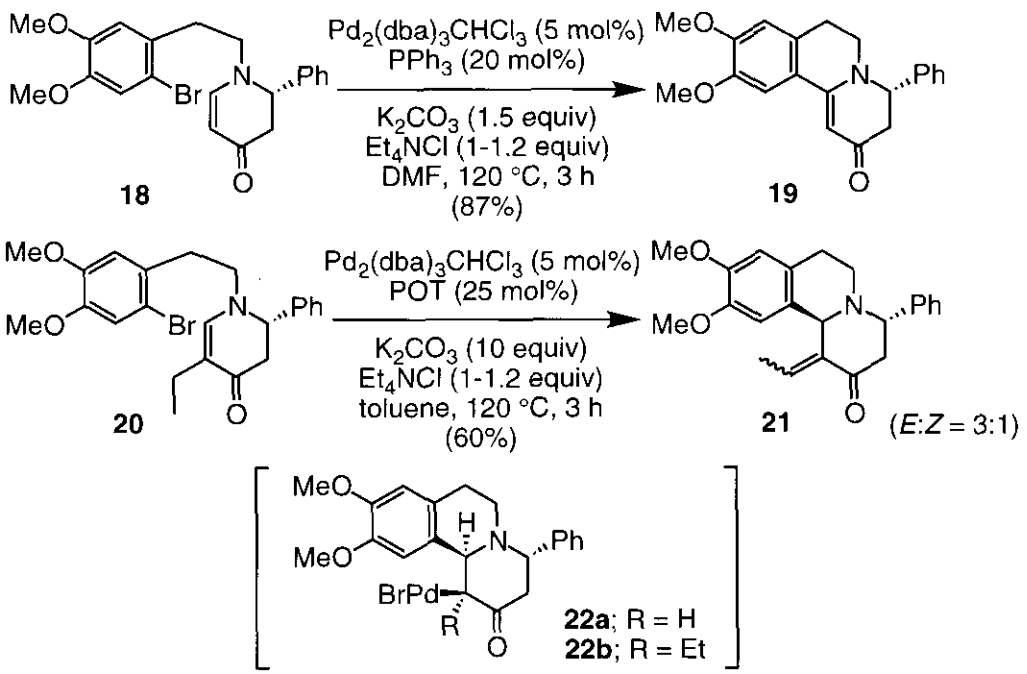


Scheme 4

Comins and coworkers reported the intramolecular Heck reaction of *N*-acyl-2,3-dihydro-4-pyridones (Scheme 5).[9] The dihydropyridone (**13**) provided **14** and **15** in 64 and 12% yields, respectively. The amido carbonyl played an important role in this reaction; in its absence, only the dehalogenated product (**17**) was isolated.



Scheme 5

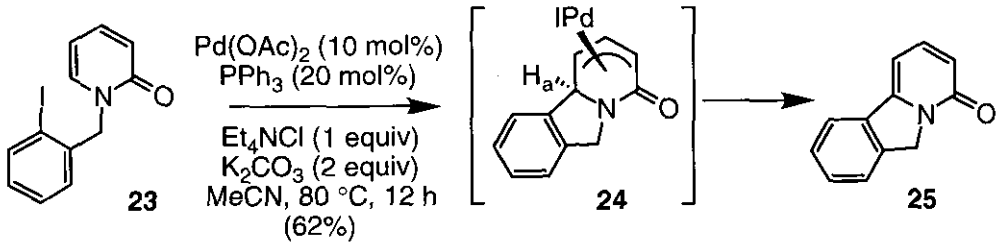


Scheme 6

In contrast, the 6-membered ring formation does not seem to require the amido carbonyl group. Waldmann and coworkers reported the construction of the tricyclic benzoquinolizine ring system by the Heck reaction of the enaminones (Scheme 6).[10] When the enaminone (**18**) was subjected to the Heck

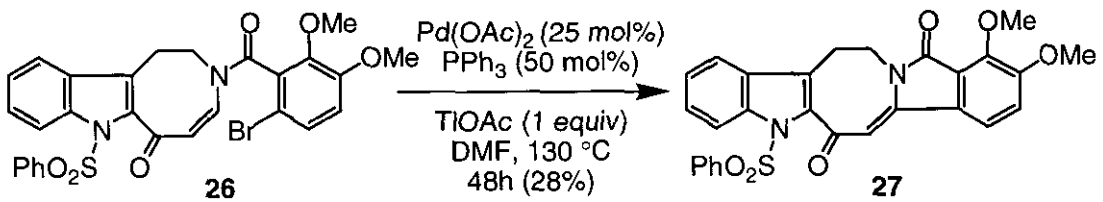
conditions, the desired tetrahydrobenzo[*a*]quinolizinone (**19**) was obtained in good yield. The best result was recorded when $Pd_2(dba)_3CHCl_3$ and PPh_3 were employed in DMF at 120 °C in the presence of K_2CO_3 and Et_4NCl. The reaction may proceed through the σ-palladium complex (**22a**) which may be converted to **19** by epimerization *via* tautomerization followed by the *syn*-elimination. In contrast, the enaminone (**20**) gave **21** embodying an exocyclic double bond in moderate yield. In this case the initially formed addition product (**22b**), due to the presence of the additional ethyl substituent, can directly eliminate HPdI probably in a *syn*-fashion by the formation of an exocyclic double bond.

The dienamide (**23**) cyclized in MeCN at 80 °C for 12 h using $Pd(OAc)_2$, PPh_3, Et_4NCl, and K_2CO_3 as a catalyst system to give **25** in a 62% yield (Scheme 7).[11] The formation of **25** requires either stereomutation of the benzylic Ha proton or the Pd-I moiety in the initial π-allyl-palladium species (**24**) to establish the necessary *cis*-relationship between Ha and the PdI moiety for the β-hydride elimination step.



Scheme 7

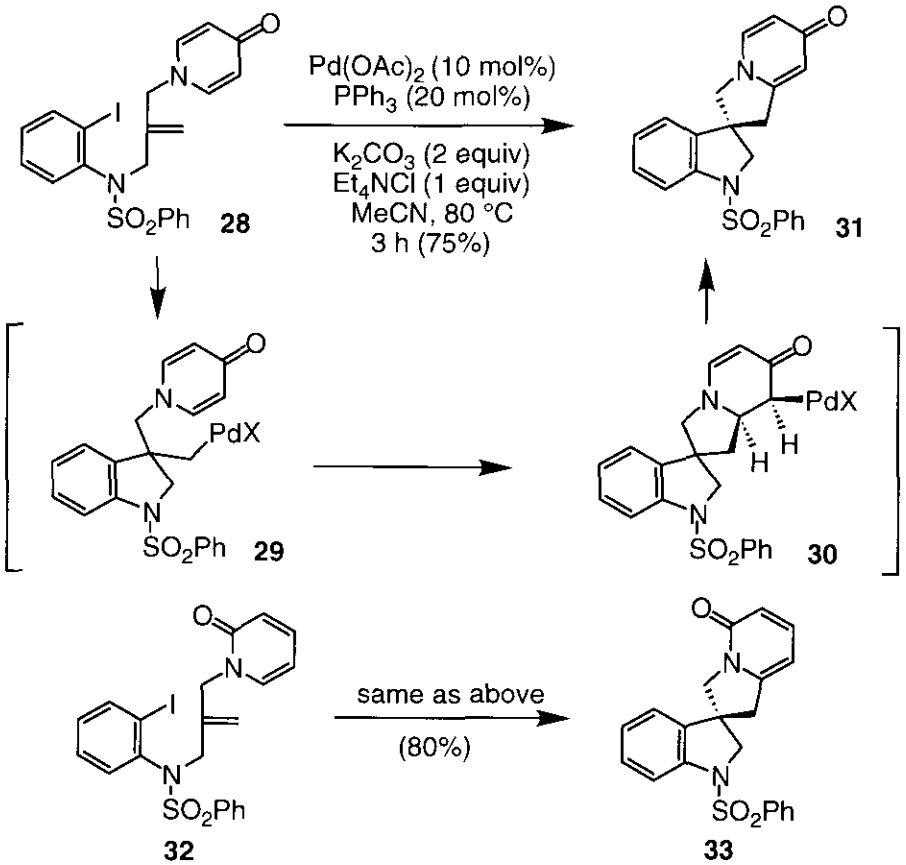
In an effort to synthesize the indole analog of magallanesine, compound (**26**) was cyclized to an isoindoloazocinoindole skeleton using a modified Heck reaction (Scheme 8).[12] Heating **26** with $Pd(OAc)_2$, PPh_3, and TlOAc in DMF at 130 °C gave the 5,14-dioxo-5*H*-isoindoloazocinoindole (**27**) in a 28% yield.



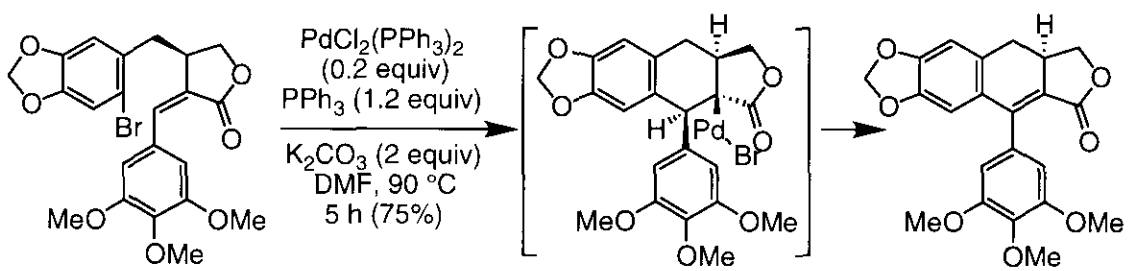
Scheme 8

An interesting tandem cyclization process including a Heck-type reaction for the synthesis of spiroindolines was reported by Grigg's group (Scheme 9).[13] The reaction of **28** under their standard conditions [$Pd(OAc)_2$, PPh_3, K_2CO_3, and Et_4NCl in MeCN] gave the spiro compound (**31**) in good yield. This reaction may proceed through alkylpalladium(II) species (**29**) produced by the first cyclization which would attack the enone system to give **30**. The formal *anti*-elimination of HPdI from **30** may afford **31**. The dienamide (**32**) also gave the spiro compound (**33**) in good yield under the same conditions.

Although all the reactions discussed above were classified as *exo-trig* cyclizations, *endo-trig* cyclizations onto the α,β-unsaturated carbonyl group have also been reported. We described the synthesis of (±)-γ-apopicropodophylline (**36**) using the 6-*endo-trig* intramolecular Heck reaction of compound (**34**) (Scheme 10).[14] The best result was obtained using $PdCl_2(PPh_3)_2$ as a catalyst in the presence of PPh_3 and K_2CO_3 in DMF at 90 °C to furnish the target compound (**36**) in a 75% yield.



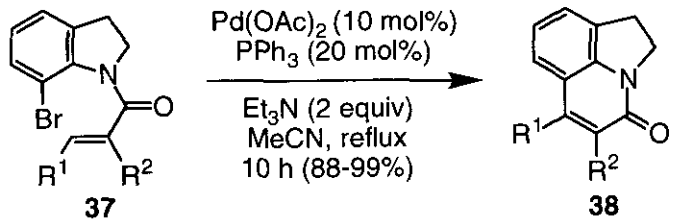
Scheme 9



Scheme 10

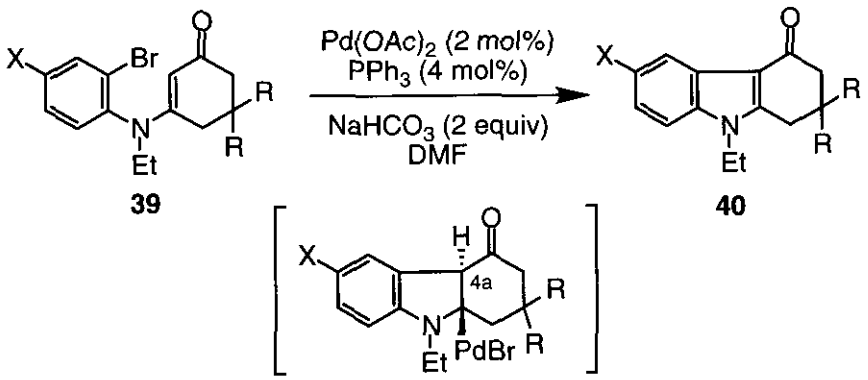
Dankwardt and Flippin also reported the 6-*endo-trig* intramolecular Heck reaction of the *N*-acryloyl-7-bromoindolines (**37**) (Scheme 11),[15] the cyclization of which proceeded efficiently to give the 6-*endo-trig*

products (**38**). No spectroscopic evidence was found for the formation of the 5-*exo-trig* product from these reactions.



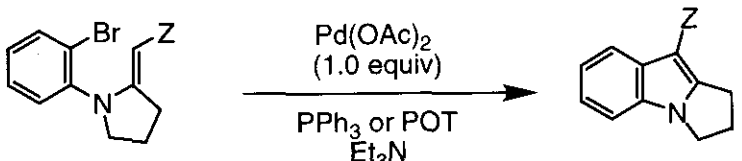
Scheme 11

Kibayashi and coworkers reported the synthesis of the carbazoles using the palladium-catalyzed 5-*endo-trig* cyclization of the enaminones (**39**) (Scheme 12).[16] When the bromoenaminones (**39**) were treated with Pd(OAc)2 and PPh3 in the presence of NaHCO3 in DMF as a solvent, the enaminone system underwent cyclization to yield the carbazoles (**40**) in moderate yields. This reaction would proceed *via* the β-palladated carbonyl intermediate (**41**), which undergoes epimerization at the 4a-position followed by a *syn*-elimination of HPdBr to give **40**.



Scheme 12

A similar study was reported on the synthesis of mitomycins starting with the *N*-(2-bromoaryl)enaminones (**42a-d**) with Pd(OAc)2 to give the pyrrolo[1,2-*a*]indoles (**43a-d**) in 55-100% yields (Scheme 13).[17]

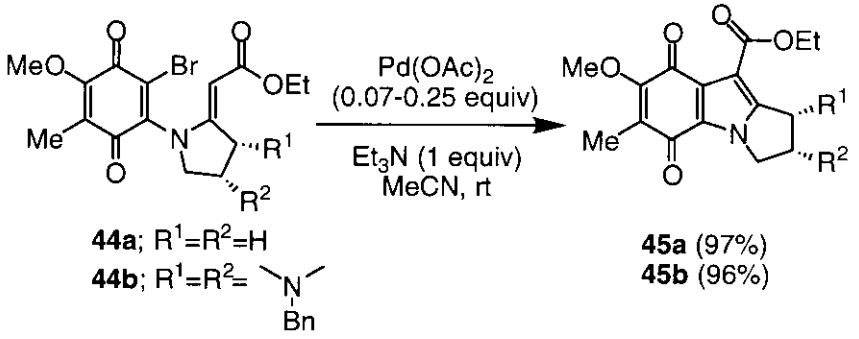


42a; Z = CO_2Et
42b; Z = COMe
42c; Z = COPh
42d; Z = CN

43a (100%)
43b (66%)
43c (79%)
43d (55%)

Scheme 13

A closer parallel was found by Rapoport and coworkers, who applied the reaction to *N*-(2-bromobenzoquinonyl) analogs (**44**) in order to obtain the quinone version of the pyrrolo[1,2-*a*]indole system directly (Scheme 14).[18,19] Thus, treatment of **44a** and **44b** with $Pd(OAc)_2$ in MeCN in the presence of Et_3N without PPh_3 gave **45a**[18] and **45b**[19] in 97 and 96% yields, respectively.



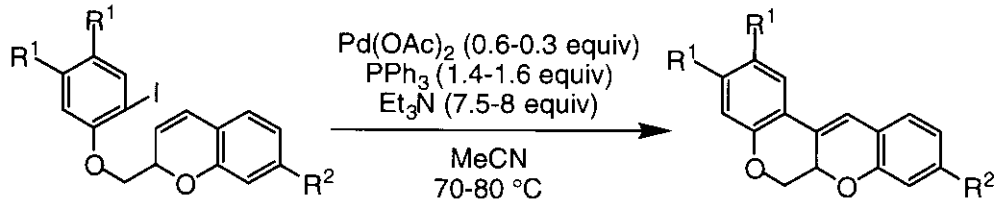
44a; $R^1=R^2=H$
44b; $R^1=R^2=$ N-Bn

45a (97%)
45b (96%)

Scheme 14

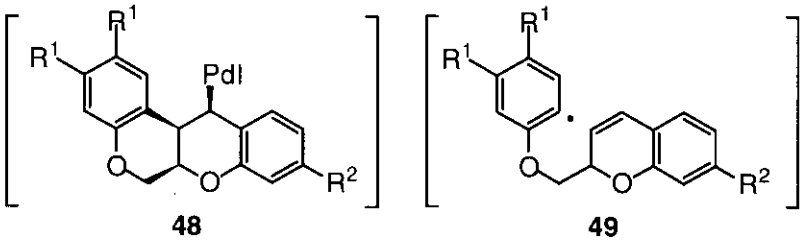
2. The Intramolecular Heck Reaction with the Styrene-type Alkenes

The chromenes (**46a-c**), upon treatment with $Pd(OAc)_2$ in the presence of PPh_3 and Et_3N in MeCN as a solvent at 70-80 °C, gave the 6,6a-dihydrorotoxen derivatives (**47a-c**) (Scheme 15).[20] Compounds (**46a-c**) would generate the intermediate (**48**) through the *syn* addition. The *syn*-elimination from **48** is stereochemically disallowed; therefore, Amos *et al.* proposed an alternative radical mechanism involving a radical intermediate (**49**). This suggestion was based on the conversion of **46a** into **47a** in 40% yield by treatment with cobalt(I) salen followed by photolysis of the resulting aryl cobalt intermediate:[21] this conversion provides some circumstantial support for the proposed radical Heck process.



46a; $R^1=R^2=H$
46b; $R^1=H$, $R^2=OMe$
46c; $R^1=R^2=OMe$

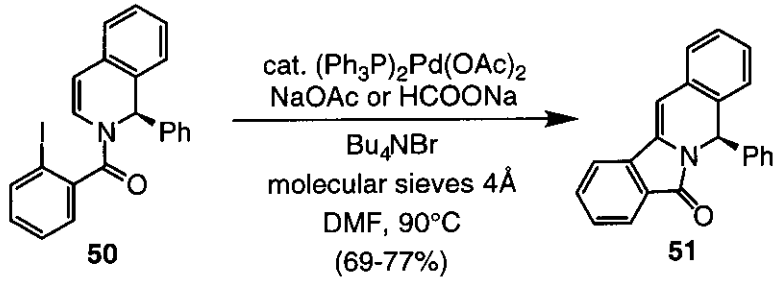
47a (58%)
47b (25%)
47c (56%)



48 **49**

Scheme 15

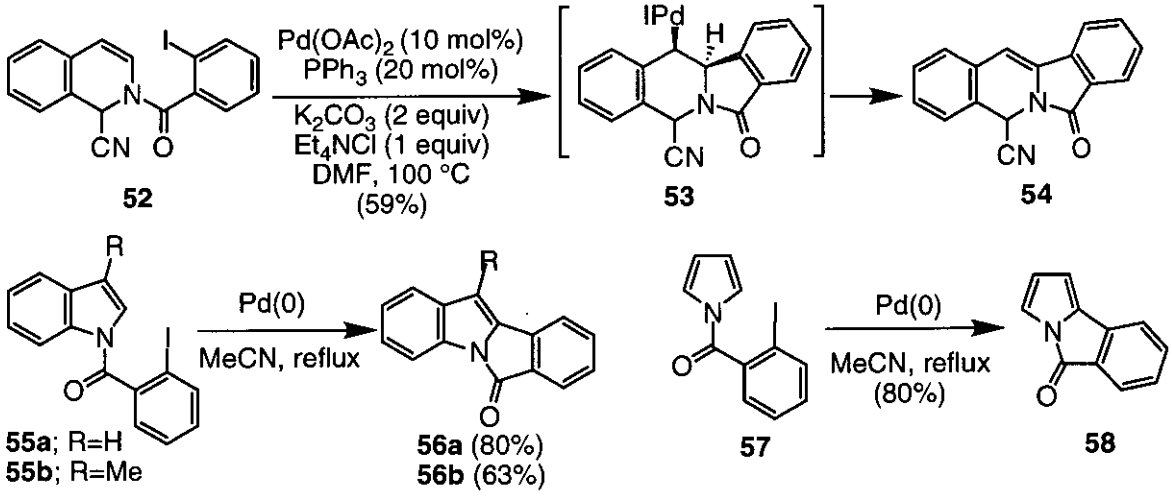
When compound (**50**) was subjected to the Heck reaction conditions, either in the presence or absence of a hydride source, **51** was the only product isolated (Scheme 16).[9] This reaction may be driven to a single product due to the extensive conjugation in **51**.



50 **51**

Scheme 16

In 1990, Grigg and coworkers reported a similar intramolecular Heck reaction (Scheme 17).[11] Using a catalyst system comprising $Pd(OAc)_2$, PPh_3, Et_4NCl and K_2CO_3 as a base, Reissert compound (**52**) was cyclized in DMF at 100 °C to **54** in 59% yield. A similar reaction of 1-aroylindoles (**55a,b**) with the same catalyst system in MeCN gave **56a,b** in 80 and 63% yields, respectively. 1-Aroylpyrrole (**57**) provides a further substrate for the intramolecular Heck reaction as illustrated by the cyclization to **58**. The expected intermediate (**53**) has the wrong stereochemistry for the required *syn*-elimination of HPdI. In this case, both the PdI moiety and a hydrogen are located at a benzylic site, and either of them undergoes a facile stereomutation furnishing the required *cis*-stereochemistry.



52 **53** **54**

55a; R=H
55b; R=Me

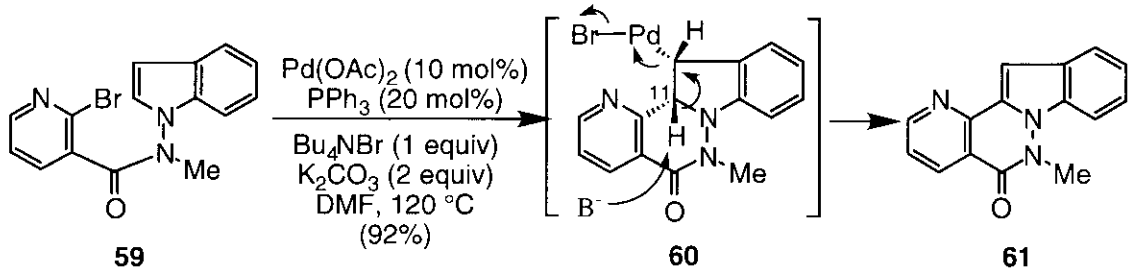
56a (80%)
56b (63%)

57 **58**

Scheme 17

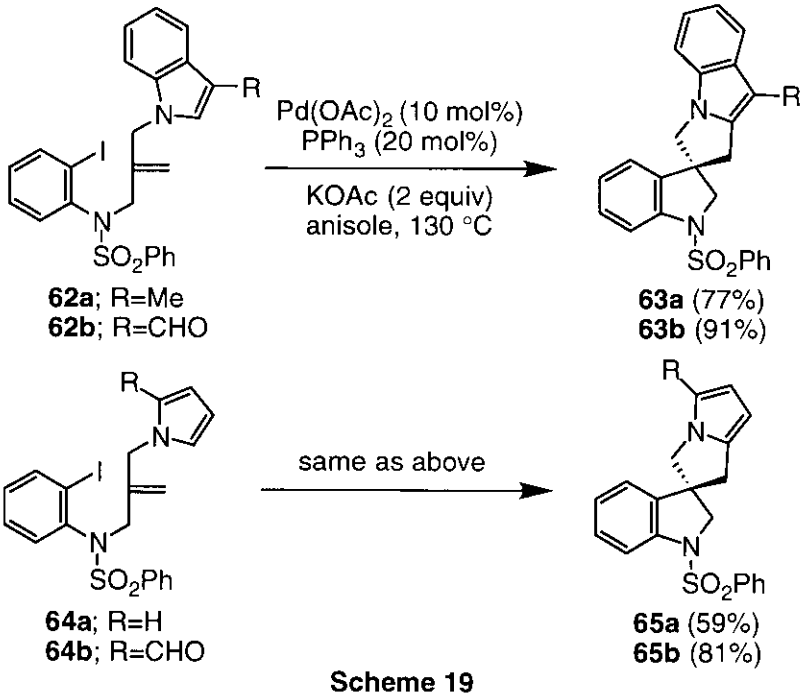
Concerning new indole analogs of pharmacological interest, Thal and coworkers used the Heck reaction to obtain a new class of heterocyclic compound, namely, pyrido[2',3'-*d*']pyridazino[2,3-*a*]indole (**61**) (Scheme 18).[22] The intramolecular Heck reaction of the *N*-methylhydrazide (**59**) under the effect of $Pd(OAc)_2$, PPh_3, Bu_4NBr, and K_2CO_3 as a base in DMF at 120 °C provided the desired tetracycle (**61**)

in a 92% yield. In the intermediate (**60**), the PdBr and a hydrogen at the 11-position are in *trans*-relationship, and so the classical β-*syn*-elimination does not occur. Melnyk *et al.* suggested that the base assisted the reductive β-elimination of the Pd species.



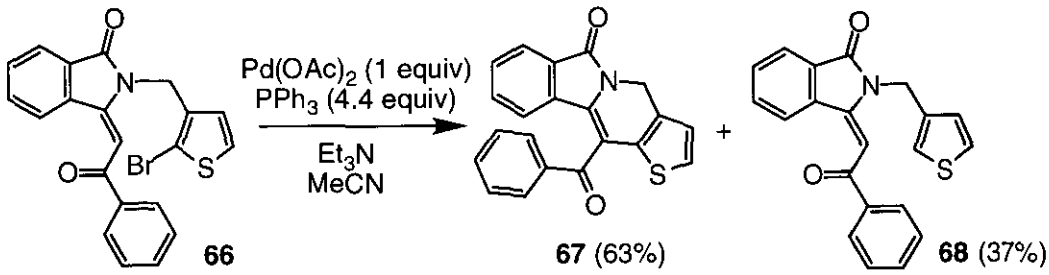
Scheme 18

Grigg and coworkers used a tandem palladium-catalyzed cyclization to construct a series of spiroindolines (Scheme 19).[13] The substrates (**62a,b**) and (**64a,b**) were treated with $Pd(OAc)_2$, PPh_3 in the presence of KOAc as a base to furnish the target spirocycles (**63a,b**) and (**65a,b**) in two successive 5-*exo-trig* processes in good to excellent yields.



Scheme 19

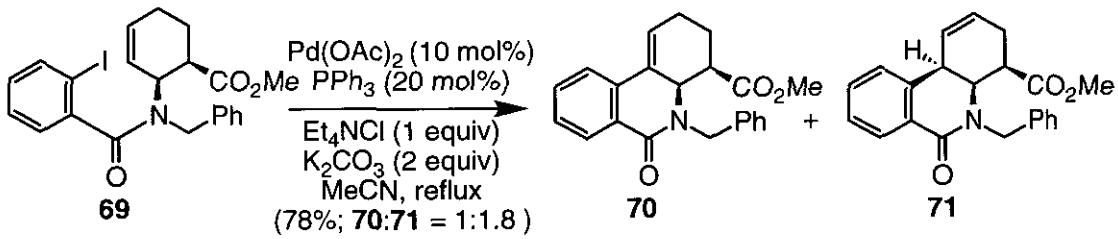
The Heck reaction conditions were applied to conversion of the (*E*)-enamidone (**66**) to the tetracyclic structure (**67**) (Scheme 20).[23] Thus **66** was treated with a stoichiometric quantity of $Pd(OAc)_2$, PPh_3, and Et_3N in refluxing MeCN for 6 days to afford **67** in a 63% yield along with compound (**68**) (37%).



Scheme 20

3. Miscellaneous Examples

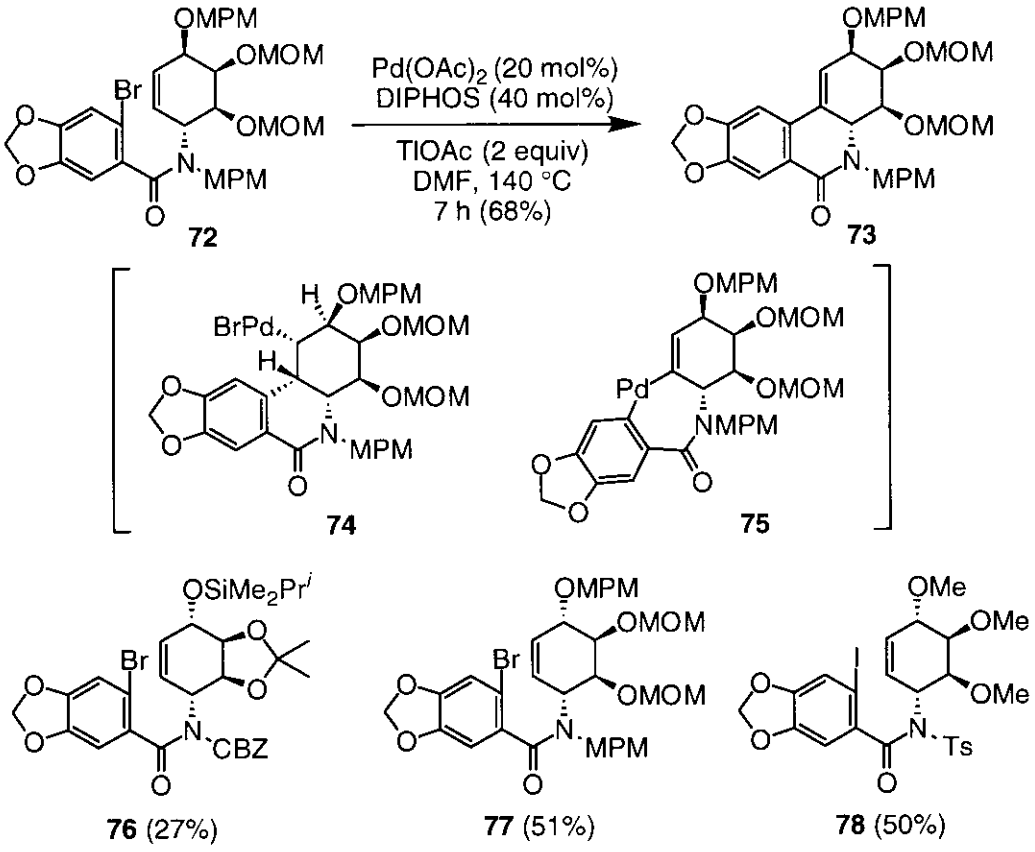
Heating **69** in MeCN at 80 °C with $Pd(OAc)_2$, PPh_3, Et_4NCl, and K_2CO_3 gave a 1:1.8 mixture of **70** and **71** in a 78% combined yield (Scheme 21).[24] The formation of **70** may involve a formal *anti*-elimination.



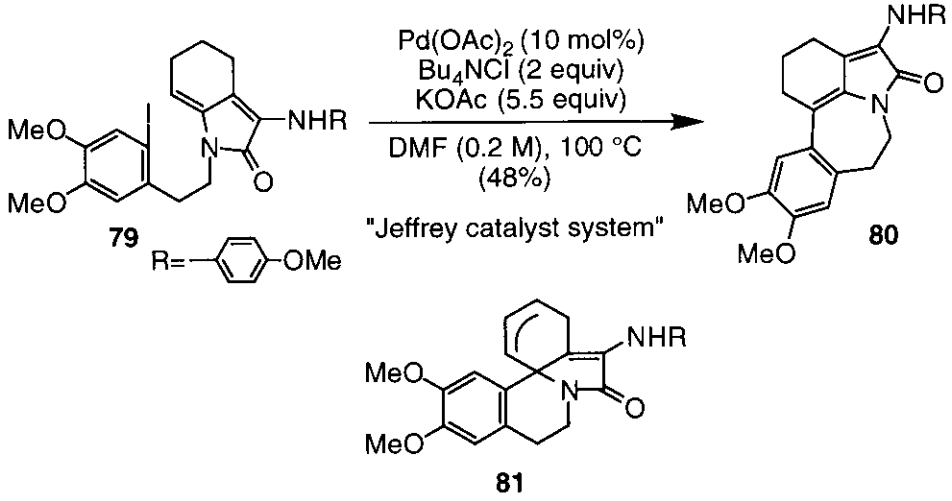
Scheme 21

The Pd-catalyzed intramolecular Heck reaction was successfully used for the construction of the phenanthridone alkaloid, lycoricidine, by four different groups (Scheme 22). Ogawa and coworkers[25] achieved the cyclization of **72** to **73** in 68% yield by means of a modified Heck cyclization with $Pd(OAc)_2$, TlOAc, and 1,2-bis(diphenylphosphino)ethane (DIPHOS) in DMF as a solvent at 140 °C. This result implies that the β-hydride elimination takes place formally with *anti* stereochemistry from the intermediate (**74**), despite of the fact that a *cis*-β-hydrogen is available. The authors suggested that a plausible intermediate was the cyclopalladated intermediate (**75**)[26] which would afford **73** selectively *via* reductive elimination of Pd. In the same way Hudlicky and Olivo[27] subjected the substrate (**76**) to cyclization in anisole to furnish the desired compound in a 27% isolated yield: desilylation was also observed. Martin and Tso[28] and McIntosh and Weinreb[29] used the same strategy for the ring closure of **77** and **78** under Ogawa's conditions to obtain the desired compounds in 51 and 50% yields, respectively.

Recently, Rigby and coworkers reported an interesting intramolecular Heck reaction of the enamide (**79**), whose regioselectivity depends upon the reaction conditions (Scheme 23).[30] Treatment of **79** under the "standard" Heck conditions [$Pd(OAc)_2$, POT, and Et_3N in $MeCN/H_2O$ (10:1) at 80 °C] afforded a mixture of the expected *exo* product (**81**) (46%) and the unanticipated *endo* product (**80**) (26%). General preference for the *exo* mode of cyclization in the intramolecular Heck reaction[31] would give **81** as the major product. Remarkably, exposure of the same enamide (**79**) to the Jeffrey palladium catalyst system[32] [$Pd(OAc)_2$, Bu_4NCl, and KOAc in DMF at 100 °C] provided only **80** in a 48% yield. The *endo* selective cyclization pathway was proved to be easily extended to the 6-*endo* (64%) and 8-*endo* (30%) cyclizations.



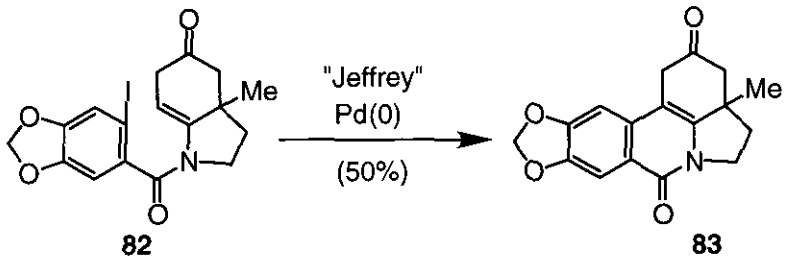
Scheme 22



Scheme 23

A new method for the formation of octahydroindole alkaloids *via* a similar intramolecular Heck reaction of the enamide (**82**) was developed by Padwa's group (Scheme 24).[33] They found that treatment of **82**

using the Jeffrey palladium catalyst system[32] provided only the pentacycle (**83**) derived from the 6-*endo* cyclization pathway in 50% unoptimized yield.



82 **83**

Scheme 24

Epilogue

It has long been believed that the Heck reaction proceeds with the *syn*-addition/*syn*-elimination mechanism. However, many examples which do not follow this general mechanism have been reported particularly in the field of the heterocyclic chemistry, although the exact mechanism is not always clarified yet. Nevertheless, the study of the Heck reaction has been expanding the scope of its applications.

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