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anti-Selective Heck-type cyclotrimerization of polycyclic bromoalkenes

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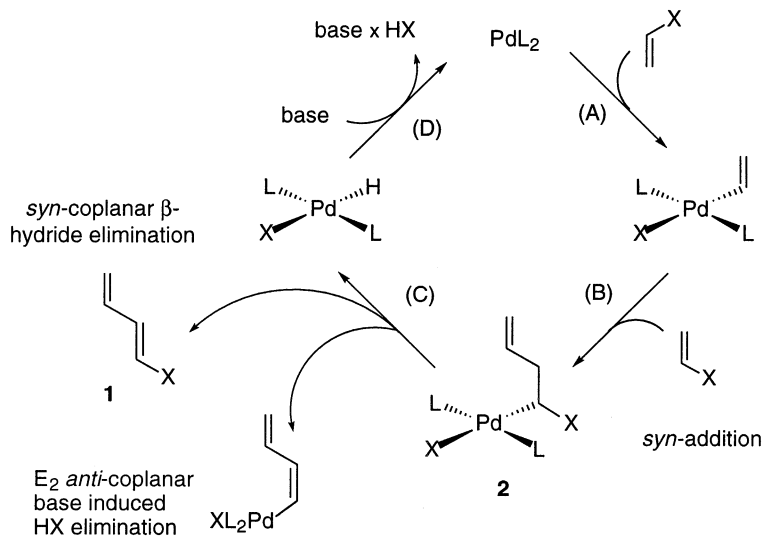
Abstract—Vinyl halides can react as both substrate and reagent in the Heck reaction. In the case of bicyclic vinyl halides, the reaction leads to cyclotrimers through an *anti*-selective process.

The addition reaction between a bromoalkene or bromoarene and an olefin in the presence of a palladium catalyst is referred to as the Heck reaction.[1] Since its discovery, the Heck reaction has been extensively exploited because of its synthetic potential and recent studies have shown that besides the traditional reagents, it is also possible with a large variety of haloalkenes or triflates and that the addition occurs even on unactivated olefins.[2] For the sake of discussion in this work, it is important to point out three features of the mechanism of Scheme 1: (i) the *syn*-addition to the olefin [step (B)], (ii) the *syn*-coplanar β-hydride elimination from the palladium σ-complex **2** [step (C)], and (iii) the need of the base to regenerate the active Pd(0) catalyst [step (D)].

Under these circumstances, one may expect that a bromoalkene may also react with itself, i.e. a bromoalkene may act both as the addend and the receiving olefin, as shown in Scheme 1. If this is indeed the case, at the stage of the palladium complex **2** the reaction may bias either towards β-hydride elimination or 'standard' base-induced E_2 elimination of HBr.



Scheme 1.

Keywords: aromaticity; cross-coupling; cyclotrimerization; Heck reaction; palladium.

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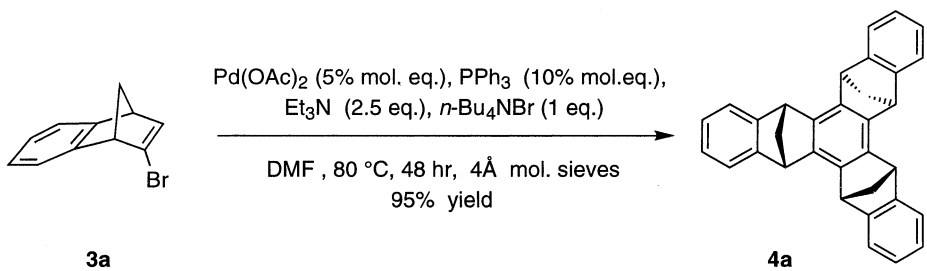
In both cases, the coupling products may continue to react with another molecule of the haloalkene in a chain process that can eventually lead to polyalkenes. We were interested in the possibility of accomplishing a dehydrobrominative cyclotrimerization reaction under Heck reaction conditions for the preparation of cup-shaped polycyclic trisannelated benzenes[3] that are promising 'host' molecules in supramolecular recognition.[4] Under the adopted reaction conditions, 5-bromo-2,3-benzonorbornadiene **3a** furnishes, stereoselectively, the *anti*-**4a** cyclotrimer in 95% yield (Scheme 2).[5]

Similarly, the bromonorbornene derivatives **3b–d** afforded the respective trimers *anti*-**4b–d** in 90–95% yields (Fig. 1).[6] Despite the fact that palladium-catalyzed dimerization, including the homo-coupling of bromoalkenes is known, it should be noted that surprisingly no formation of dimers was observed in the presented cases, even in reactions stopped at an early stage.

Tetraalkylammonium salts efficiently enhance the rate of the Heck reactions.[2b,7] While the above reactions carried out without added ammonium salts proceed very slowly (7 days, 80°C, 70% conversion), the reactions carried out in the presence of n-Bu_4NHSO_4, as well as n-Bu_4NCl, or n-Bu_4NBr, reach completion within 48 h. Furthermore, replacing the bromine with an iodine atom does not significantly effect the composition of the product mixture. 2-Iodobenzonorbornadiene affords, under similar reaction conditions, only the *anti*-trimer **4a** in comparable yields.

As shown in Scheme 3, the formation of complex **6** accounts for the hypothesis of base-induced E_2 elimination of HBr at the stage of the σ-complex **5** (as previously proposed in Scheme 1) because it cannot undergo a *syn*-coplanar β-hydride elimination. Complex **6** then may carbopalladate another molecule of bromoalkene to afford the cyclic trimer **7** which undergoes 6π electrocyclization to the cyclic trimer **8** and subsequently elimination as in the standard Heck reaction.

The almost exclusive formation of the *anti*-trimer also calls for an explanation, because the reaction of a racemic mixture of bromoalkene should afford a statistical 3:1 mixture of *anti*-plus *syn*-trimers.[3] In fact, the reaction of the (*R*) enantiomer of the bromoalkene with a homochiral counterpart would lead to a *syn*-dimer **6** (path A in Scheme 4) while that with the heterochiral bromoalkene would lead to the *anti* isomer (path B in Scheme 4).[3c] While the latter can exclusively lead to the *anti*-trimer, the *syn*-dimer **6** may react with the homochiral bromoalkene to afford the *syn*-trimer while with the heterochiral enantiomer it would again afford the *anti*-trimer, thus establishing the 3:1 statistical mixture.



Scheme 2.

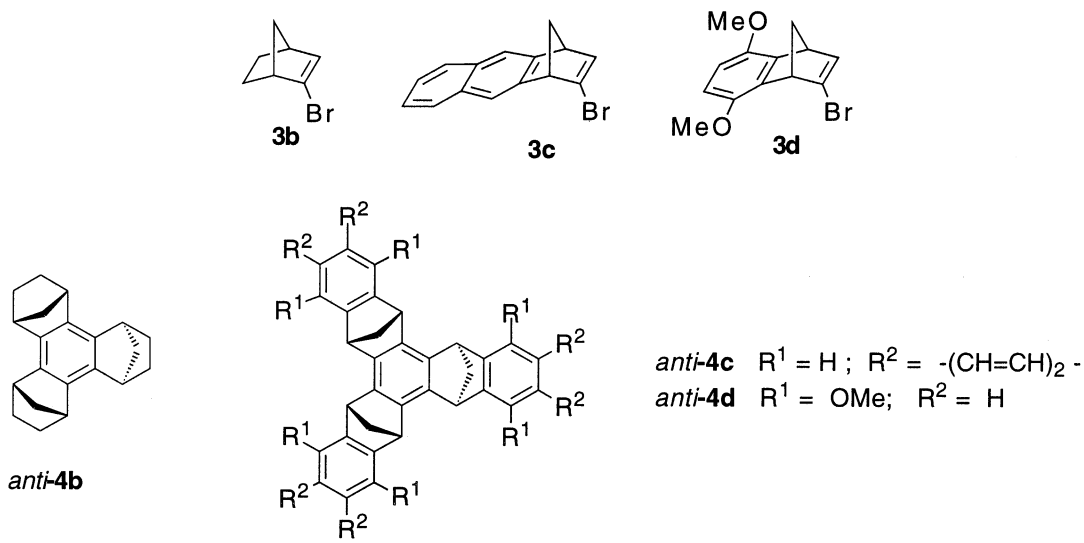
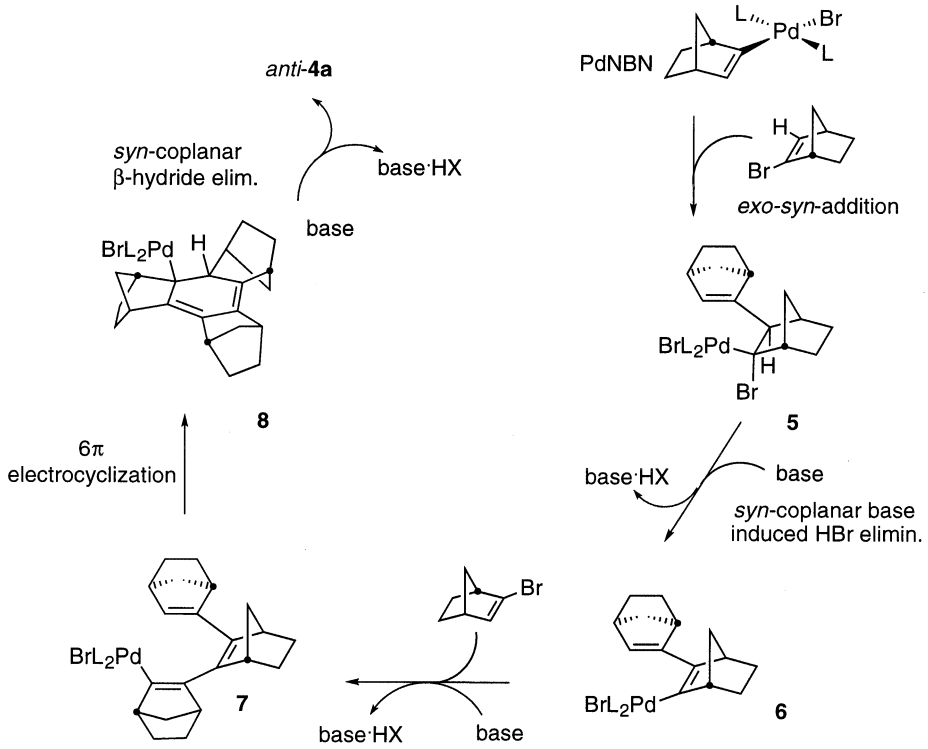
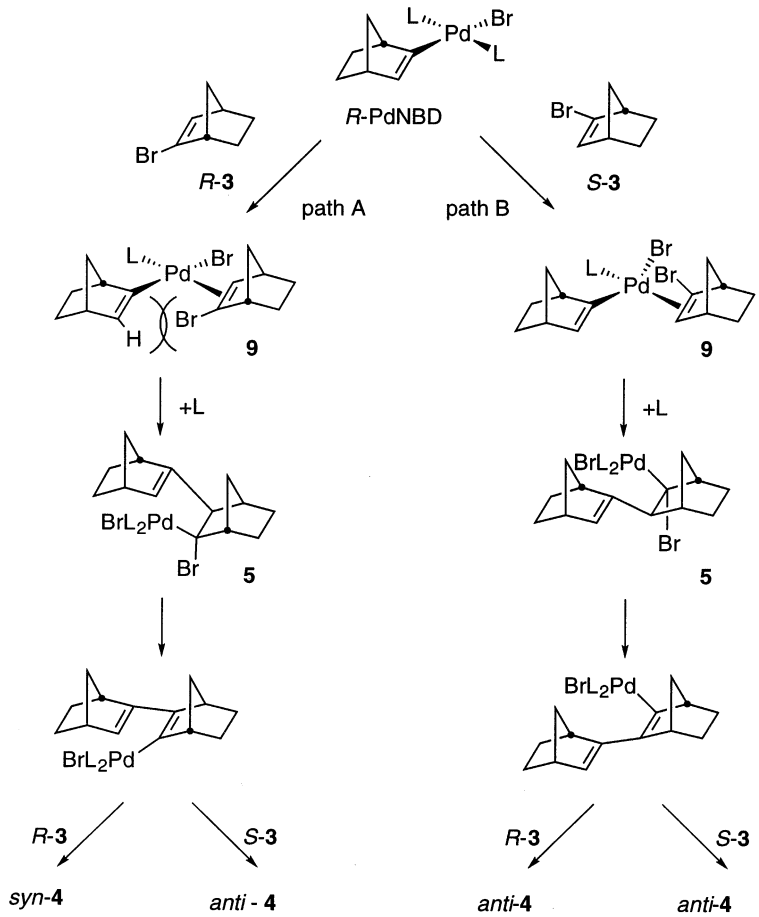


Figure 1.



Scheme 3.



Scheme 4.

The origin of the stereoselectivity must be attributed to the steric overcrowding in the neutral complex (*R,R*)-**9** (or *S,S*-**9**) which is also eventually repeated in the second addition to the dimer **6** and for these reasons none of either the expected *syn*-dimer **6** or the *syn*-trimer **4** was observed. In order to assess the fact that the *syn*-trimer **4** does not form due to a higher energy path, the reaction was performed with the enantiopure 5-bromo-2,3-benzononorbornadiene **3a**.[8] The transformation of this proceeded much more slowly than that carried out with the racemate, affording a mixture of *syn*- and *anti*-trimers **4** in ca. 3:1 ratio together with substantial amounts of unidentified products, and not the pure *syn*-trimer as expected along path A of Scheme 4. Thus, the transformation of a single enantiomer requires a higher activation energy and probably proceeds via a symmetric metal complex, the corresponding strained bicyclic acetylene,[9] in which the chiral information is lost.

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5. *Typical experimental procedure*: A suspension of Et_3N (0.35 g, 3.5 mmol) *n*-Bu_4NBr (0.451 g, 1.4 mmol), powdered 4 Å molecular sieves (0.6 g) and freshly dried DMF (1.5 mL) was stirred at room temperature under argon. After 15 minutes the appropriate vinyl bromide **3** (1.4 mmol) and PPh_3 (0.14 mol, 10% mol equiv.) were added in that order and the resulting suspension was stirred for an additional 15 minutes, $Pd(OAc)_2$ (0.07 mmol, 5% mol equiv.) was then added and the mixture was stirred at 80°C reaching completion after 48 h (monitoring by NMR). After cooling to room temperature, diethyl ether (60 mL) was added and the organic phase was washed with water (3×30 mL) and brine (3×30 mL), dried ($MgSO_4$) and concentrated at reduced pressure. The residue was purified by flash chromatography (eluant: *n*-hexane–ethyl acetate in a 98:2 ratio).
6. For *anti*-**4a**: see Ref. 3c. For *anti*-**4b**: see Ref. 3j. For *anti*-**4c**–**e**: see Ref. 3b.
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8. Enantiopure reagent **3a** is obtained by resolution of the racemate by HPLC chiral separation on Chiralcel OT(+), eluant methanol.
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