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Palladium Catalyzed 1,8-Conjugate Addition to Heptafulvene *via* Bis-π-allyl Palladium Complexes

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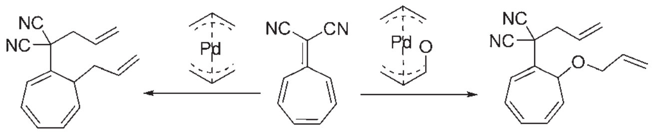
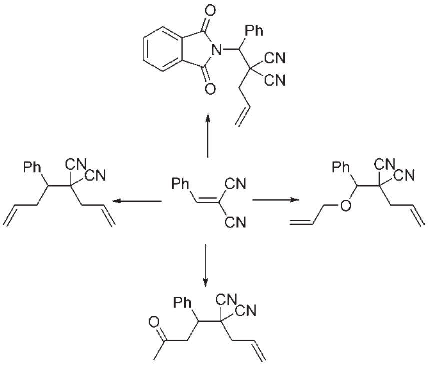
ABSTRACT



The palladium catalyzed 1,8-conjugate addition of heptafulvene, an antiaromatic conjugated 8π-electron system, is discussed. The method is utilized for the concise synthesis of bis-functionalized cycloheptatriene (CHT) derivatives. This is the first report on the palladium catalyzed bisfunctionalization of a cyclic cross conjugated system.

Transformations utilizing bis-π-allylpalladium complexes represent one of the most important areas of homogeneous catalysis.[1] Over the past two decades, bis-π-allylpalladium and related complexes have effectively been utilized for the functionalization of highly activated olefins. These olefins undergo efficient bis-functionalizations including bis-allylation,[2] alkoxy-allylation,[3] cyano-allylation,[4] acetonation-allylation,[5] amino-allylation,[6] and alkyl-allylation[7] to afford α,β-functionalized products in high yields under mild conditions with high atom economy (Scheme 1). We recently described an efficient synthesis of 3,3-disubstituted indole-2-ones from isatylidenes by utilizing amphiphilic bis-π-allylpalladium and related intermediates.[8]

Scheme 1. Bis-Functionalization of Dicyanostyrene



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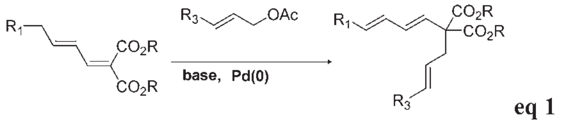
An isolated study on palladium(0) catalyzed deconjugative allylation in a conjugated sysem was reported for the first time by the research group of Sato.[9] They carried out the reaction on alkenylidenemalonate with allyl acetate in the presence of Pd to afford a 1,3-diene unit attached to a quaternary carbon center (eq 1).



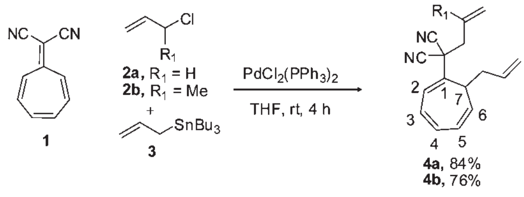
eq 1

Conjugate addition to activated alkenes has been extensively studied, as evidenced by the large number of publications on the subject.[10] In contrast, higher order conjugate additions such as 1,8-addition to extended or cyclic conjugated systems remains underdeveloped,[11] with absolutely no precedent for Pd-catalyzed 1,8-conjugate addition. This fact combined with our interest in bis-π-allylpalladium chemistry prompted us to investigate its reactivity on activated olefins. Our choice of olefin was heptafulvene. Heptafulvenes, fundamental members of nonalternant conjugated compounds, have been promising candidates for functional uses in view of their peculiar conjugated π-structure.[12] Various properties of heptafulvene and its derivatives including cycloaddition reactions,[13] dependence on substituent nonlinear optical activity,[14] through-resonance effect in 8-substituted heptafulvene derivatives,[15] *etc.* have been the subject of several investigations. Among the electron-deficient heptafulvenes, 8,8-dicyanoheptafulvenes are the most studied, and limited information reveals that it elicited all possible modes of reactivity in cycloadditions (i.e., as 2π, 4π, 6π, or 8π components).[16]

Apart from a single report on the Negishi coupling on 8,8-dicyanoheptafulvene,[17] leading to phenyl heptafulvene, there has been no report on the palladium catalyzed reactions involving heptafulvenes. We report herein the palladium catalyzed 1,8-conjugate addition on 8,8-dicyanoheptafulvene leading to disubstituted cycloheptatriene (CHT) derivatives. We have also ascertained the regiochemistry of the above-mentioned CHT derivatives using Diels–Alder cycloadditions with triazolinediones.

Our first attempt to explore the reaction of 8,8-dicyanoheptafulvene (**1**) with allyl chloride (**2a**) and allyl tributylstannane (**3**) employed 5 mol % $PdCl_2(PPh_3)_2$, under an argon atmosphere in THF at room temperature, reaction conditions that were used in our earlier report on palladium catalyzed bis-functionalization of isatylidenes.[8] The described cycloheptatriene derivative **4a** was obtained in 84% yield (eq 2). The reaction of **1** with methallyl chloride **2b** also afforded the corresponding CHT derivative **4b** in 76% yield.

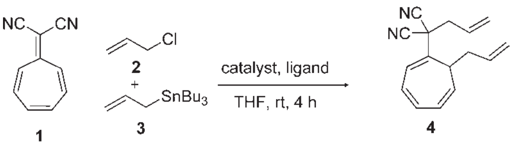
Palladium catalyzed bis-allylation of disubstituted heptafulvene



eq 2

A series of palladium sources and ligands were screened in an effort to obtain better reaction conditions (Table 1). Decreasing the catalyst loading in the original $PdCl_2(PPh_3)_2$ system led to an incomplete reaction. Catalysis by Pd(PPh_3)$_4$ was also found to be good, but the reaction rate was considerably decreased.

Table 1. Optimization Studies of Bis-allylation of Dicyanoheptafulvene[a]



entry	catalyst	ligand	mol % of catalyst	yield %
1	$PdCl_2(PPh_3)_2$	–	5	84
2	$PdCl_2(PPh_3)_2$	–	3	53
3	$PdCl_2$	PPh_3	5	No reaction
4	$Pd(OAc)_2$	PPh_3	5	No reaction
5[b]	$Pd(PPh_3)_4$	–	5	70
6	$Pd_2(dba)_3 \cdot CHCl_3$	–	5	No reaction
7	$Pd_2(dba)_3 \cdot CHCl_3$	PPh_3	5	45
8	$(Pd(allyl)Cl)_2$	PPh_3	5	No reaction

[a] Reaction conditions: heptafulvene (1.0 equiv), allyl chloride (2.0 equiv), allyl tributyl stannane (2.0 equiv), THF, rt, 4 h. [b] Heptafulvene (1.0 equiv), allyl chloride (2.0 equiv), allyl tributyl stannane (2.0 equiv), THF, rt, 8 h.

From optimization studies, the combination of 8, 8-dicyanoheptafulvene (1.0 equiv), allyl chloride (2.0 equiv), allyl tributylstannane (2.0 equiv), and $PdCl_2(PPh_3)_2$ (5 mol %) in 2 mL of THF at room temperature under an argon atmosphere gave the best results.

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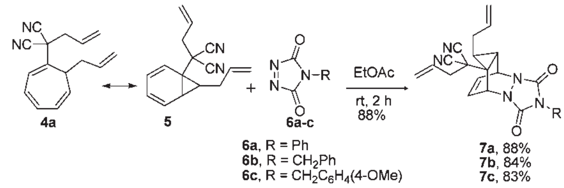
In the ^{1}H NMR of **4a**, a sufficient number of allylic protons were discernible at the typical regions: sp^3 CH$_2$'s as three multiplets at δ 1.85, 2.08, and 2.75; methynyl CH appearing as a multiplet at δ 5.75; methenyl CH$_2$ at δ 5.40 and 4.97. The sp^2 ring protons resonated as three multiplets at δ 6.66, 6.50, and 6.31 and as a triplet at δ 5.57. The sp^3 ring proton on the other hand appeared as a multiplet at δ 3.32. However, the ^{1}H NMR spectrum remained inconclusive as to the position of the two allylic substituents on the CHT ring. To ascertain the regiochemistry of the CHT derivative **4a,** we employed a Diels–Alder cycloaddition strategy to trap norcaradiene **5**, the valence tautomer of 1,3,5-cycloheptatriene **4a**, with *N*-phenyl-1,3,5-triazoline-2,4-dione **6a** (PTAD) as the dienophile. This was based on the fact that the position of allylic substituents on CHT could be deduced from the structure of the cycloadduct obtained.[18] Accordingly, when we reacted CHT **4** with PTAD **6a** in ethyl acetate for 2 h at room temperature, the reaction afforded the cycloadduct **7** in 88% yield (eq 3).

Diels-Alder cycloaddition of bis-allylated CHT derivative.

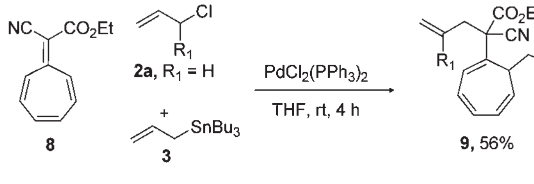


eq 3

Evidence for structure **7a** was readily apparent from the ^{1}H NMR spectra which, in addition to the expected proton resonances, displayed the two key protons of the cyclopropane ring as two multiplets at δ 2.20 and 1.61. The structure was further confirmed from the ^{1}H–^{1}H COSY spectrum. Finally, the mass spectrum showed a molecular ion peak at m/z 412.40 (M + 1), which supported the assigned structure. The formation of **7a** authenticated the structure of **4** to be the 1,7-disubstituted CHT derivative.

The heptafulvene **8** derived from ethyl cyanoacetate also showed similar reactivity toward the bis-π-allyl palladium complex derived from allyl chloride **2a** and allyl tributyltin **3** and yielded the corresponding bis-allylated CHT derivative **9** in 56% yield (eq 4).

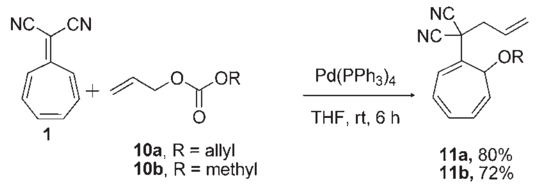
Palladium catalyzed bis-allylation of **8**



eq 4

The possibility of utilizing an oxa-π-allyl-π-allyl palladium complex, an unsymmetric functionalized version of the amphiphilic bis-π-allyl palladium intermediate, for the alkoxy-allylation[19] of 8,8-dicyanoheptafulvene was then explored. Dicyanoheptafulvene **1** on reaction with 2.5 equiv of diallyl carbonate **10a**, the precursor for the oxa-π-allyl-π-allyl palladiuim intermediate, in the presence of 5 mol % of Pd(PPh$_3$)$_4$ as a catalyst and THF as the solvent at room temperature afforded the expected allyl-*O*-allyl product **11a** in 80% yield (eq 5). With allylmethyl carbonate **10b**, dicyanoheptafulvene **1** afforded the corresponding methoxy substituted CHT derivative **11b** in 72% yield.

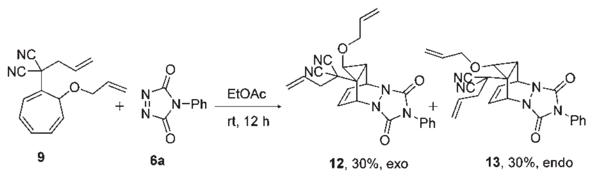
Alkoxy-allylation of dicyanoheptafulvene



eq 5

The regiochemistry of **11a** was established utilizing the Diels–Alder reaction of **11a** with *N*-phenyl-1,3,5-triazoline-2,4-dione **6a**. The cycloaddition offered an equimolar mixture of exo and endo isomers **12** and **13** (eq 6).

Diels-Alder reaction of Allyloxy-allylated CHT

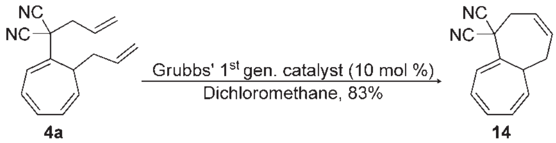


eq 6

The ^{1}H and ^{13}C NMR spectra of **12** and **13** were completely in agreement with the proposed structure. The exo and endo isomers were distinguished on the basis of coupling constants (J_{trans} = 2.0 Hz ; J_{cis} = 6.0 Hz) observed for the *cis* and *trans* cyclopropane ring protons.

After establishing the structure and regiochemistry of the bis-functionalized products, we explored the synthetic potential of one of the products toward the synthesis of heptalene.[20] Heptalenes are of considerable pharmaceutical relevance, as the members of this family such as colchicine[21] which act as a potent drug against gout. The ring closing metathesis[22] of **4a** using Grubbs' first generation catalyst resulted in the formation of dicyanotetrahydroheptalene **14** in 83% yield (eq 7).

Ring Closing Metathesis of bis-allylated CHT derivative



eq 7

In conclusion, we have developed a concise synthesis of bis-functionalized CHT derivatives *via* palladium catalyzed

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1,8-conjugate addition of dicyanoheptafulvene and disclosed its structure by means of a Diels–Alder cycloaddition strategy. The bis-functionalization reaction reported here is the first application of palladium catalyzed reactions on a cyclic conjugated system. Further work aimed at utilizing this developed method for the bis-functionalization of other cyclic conjugated systems is in progress.

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Supporting Information Available. Experimental procedures, characterization data, and spectra of products. This material is available free of charge via the Internet at http://pubs.acs.org.