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A New Pd-Catalyzed Cascade Reaction for the Synthesis of Strained Aromatic Polycycles

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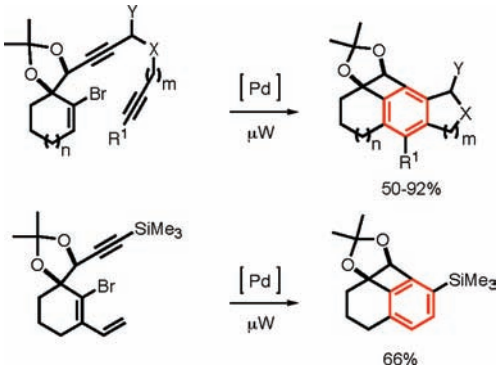
ABSTRACT



Two new palladium catalyzed cascade reactions involving a 4-*exo*-dig cyclocarbopalladation are described. These processes are shown to convert bromoenediynes and bromodienynes into strained aromatic compounds in a single step.

The generation of complex molecules from simple starting materials in a minimum number of steps is one of the most challenging goals in organic synthesis.[1] Toward this end, cascade reactions using transition-metal-catalyzed processes have become powerful tools for the construction of functionalized polycyclic molecules.[2] In particular, the development of new methods to generate cyclooctanoid ring systems remains an attractive objective.[3] Along those lines, we have disclosed an efficient process that leads to the formation of unusual polycyclic compounds through an initial 4-*exo*-dig cyclocarbopalladation of bromopropargylic diols.[4] Specifically, we have shown that a 4-*exo*-dig cyclocarbopalladation, followed by a Stille cross-coupling, and finally a concerted conrotatory 8π electrocyclization allows the preparation of highly functionalized tetracyclic compounds containing an eight-membered ring.[5]

In an effort to extend this method, we examined an intramolecular version of this reaction sequence. As illustrated in Scheme 1, three different cascades were envisaged. Depending on the substrate, an initial 4-*exo*-dig, followed by a 5-*exo*-dig, cyclocarbopalladation should lead

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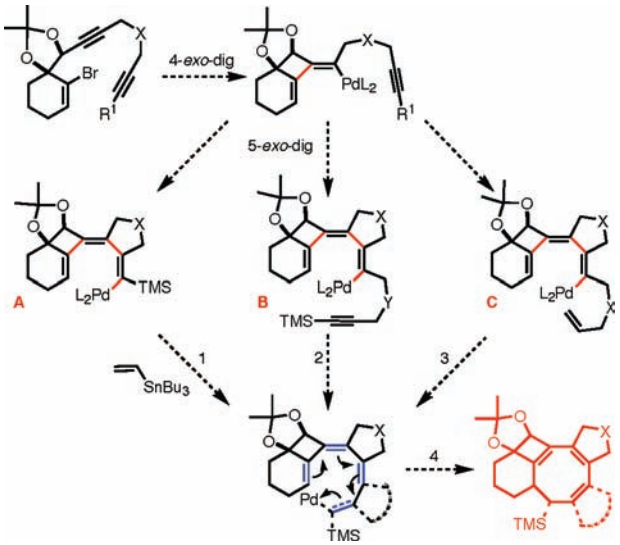
Scheme 1. Strategies for the Synthesis of Cyclooctanoids[a]



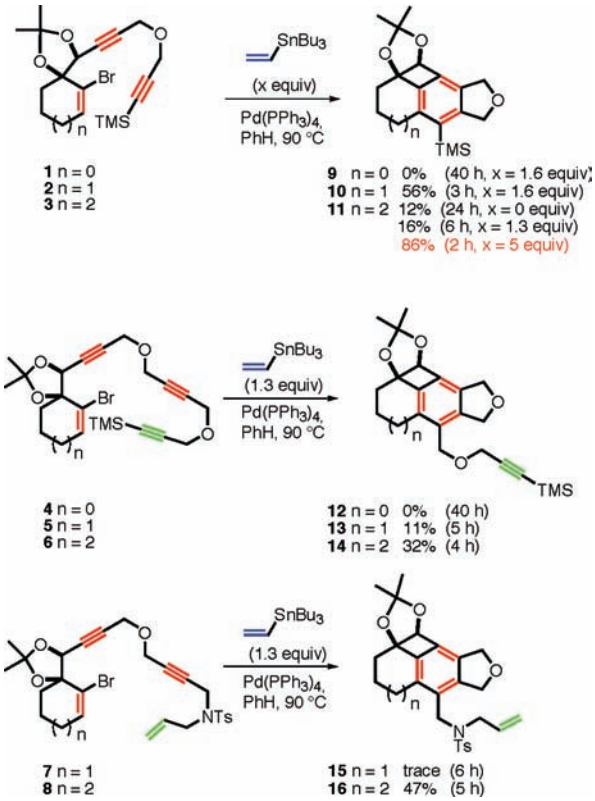
[a] (1) Stille cross coupling, (2) 5-*exo*-dig, (3) 5-*exo*-trig, (4) 8π electrocyclization.

to the palladated trienes of type **A**, **B**, or **C**. Then, a Stille cross-coupling (path 1), 5-*exo*-dig cyclocarbo-palladation (path 2), or 5-*exo*-trig cyclocarbopalladation (path 3) should occur, which in all cases would be terminated by an 8π electrocyclization (path 4) to give the expected cyclooctanoid compounds.

As shown in Scheme 2, when substrates **1**−**8** were treated with vinyltributylstannane in the presence of $Pd(PPh_3)_4$ (10 mol %) in benzene at 90 °C, the expected eight-membered ring-containing products were not observed. Instead, several unique polycyclic aromatic ring-containing systems (**10**−**11**, **13**−**14**, and **16**) were isolated as the main products of this transformation. The structures of these new compounds were determined through a combination of 1D and 2D ^{1}H and ^{13}C NMR experiments. The fused four-membered ring embedded in each of these products suggested that initial 4-*exo*-dig cyclocarbopalladation had proceeded as expected; however, the subsequent transformations may have deviated from the pathway outlined in Scheme 1.

During optimization studies, it was noted that several structural features were required to obtain higher yields. First, a terminal trimethylsilyl group on the alkyne is required to obtain the aromatic product; indeed, only decomposition of the starting material was observed if a terminal alkyne compound was used. Second, the five-membered ring-protected diol **1** did not give any product even after 40 h of reaction ($n = 0$, starting material). Moreover, the reaction appeared to be dependent on the amount of vinyltributyl-stannane used. Without it, or when used in small quantities, the yield of the reaction decreased significantly (**11**, 12%, 16%). In comparison, when used in excess (5 equiv), the reaction provide product **11** in 86% yield. Although not incorporated into the final product, the vinyltributylstannane appears necessary for the catalytic cycle to proceed ef-

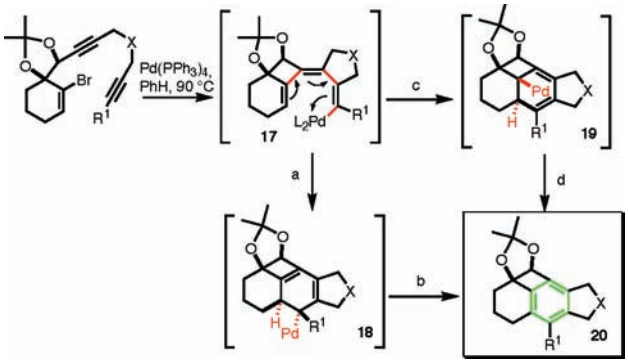
Scheme 2. First Experiments



ficiently. We expect the vinylstannane is serving as either a base or reducing agent in this transformation (vide infra).

These results were not expected but are understandable. Of the several mechanistic possibilities, two are suggested in Scheme 3. Indeed, instead of realizing the Stille cross

Scheme 3. Possible Mechanisms



[a] 6π electrocyclization. [b]Syn dehydropalladation elimination. [c]Heck addition. [d]Anti dehydropalladation elimination.

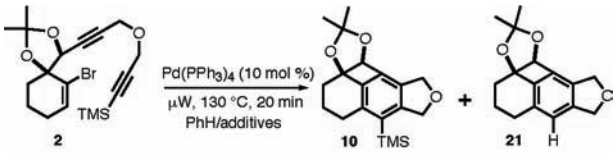
coupling (path 1, Scheme 1), or the second 5-*exo*-dig (path 2) or 5-*exo*-trig (path 3), a concerted disrotatory 6π electrocyclization on the palladated triene **17** occurred. The hydrogen and the palladium are in a cis configuration in **18**, allowing a syn dehydropalladation elimination and giving

the final strained aromatic derivatives **20** (path a and b, Scheme 3). A second mechanism is also possible; the reaction could occur via a Heck-type addition after the initial 4-*exo*-dig and 5-*exo*-dig cyclocarbopalladation. In this case, a rare but known anti dehydropalladation elimination on **19** could be operative (paths c and d, Scheme 3).[6]

In the past, regioselective construction of polysubstituted aromatics has been achieved mainly through stepwise introduction of substituents via electrophilic substitutions or cross-coupling reactions. These are useful methods, but particularly in the case electrophilic substitutions, high regioselectivity can only be achieved by careful choice of reagents and synthetic route. Alternatively, transition-metal-catalyzed approaches employing single operation tricyclizations of bromoenediynes have been used to prepare carbocyclic, as well as heterocyclic, angularly bis-annelated benzene derivatives,[1d,7] but none begin with a 4-*exo*-dig cyclocarbopalladation, a transformation that eventually leads to functionalized and highly strained products.

In our initial experiments, we showed that the vinyltributylstannane was necessary but not incorporated into the product. As it may act as a base that regenerates the active palladium species, we decided to replace the stannane with organic bases. Several organic amines were tested (Table 1). The most efficient additive was diisopropylamine, which gave product **10** in 89% yield, as well as a small amount of the desilylated compound **21**.

Table 1. Reaction Optimizations



additives	yield	ratio **10**/**21**	additives	yield	ratio **10**/**21**
$SnBu_3$ (1.6 equiv)	87%[a]	89/11	PhH / *i*-Pr_2NEt 2 / 1 : 0.02 M	48%	100/0
PhH / *i*-Pr_2NH 2 / 1 : 0.02 M	89%	89/11	PhH / morpholine 2 / 1 : 0.02 M	47%	100/0
PhH / *i*-Pr_2NH 2 / 1 : 0.1 M	77%	93/7	PhH / pyrrolidine 2 / 1 : 0.02 M	33%	100/0
Et_3N (1 equiv)	42% + 41% of **2**	80/20			

[a] Thermic conditions: $Pd(PPh_3)_4$ 90 °C, 3 h gave only 56% yield.

We reported previously that the yield of the 4-*exo*-dig cyclocarbopalladation was improved by the use of microwave irradiation while also shortening the reaction time.[4d] A much cleaner reaction was observed for these substrates as well under these conditions. Microwave irradiation of compound **2** with $Pd(PPh_3)_4$ (10 mol %) for 20 min at 130 °C in a mixture of benzene and diisopropylamine gave a significant improvement in the final yield. Different reaction concentrations were used (0.02 or 0.1 M), and the results were similar, although less desilylation byproducts were observed at the high concentrations.

As summarized in Figure 1, a variety of substrates were treated under the optimized conditions to provide the aromatic compounds in 50−92% yields. After the 4-*exo*-dig cyclocarbopalladation, a 6-*exo*-dig cyclocarbopalladation followed by aromatization was shown to lead to products **22**, **26**, and **27**, or alternatively, a 7-*exo*-dig cyclocarbopalladation followed by aromatization provided the seven-membered ring-containing product **23**.

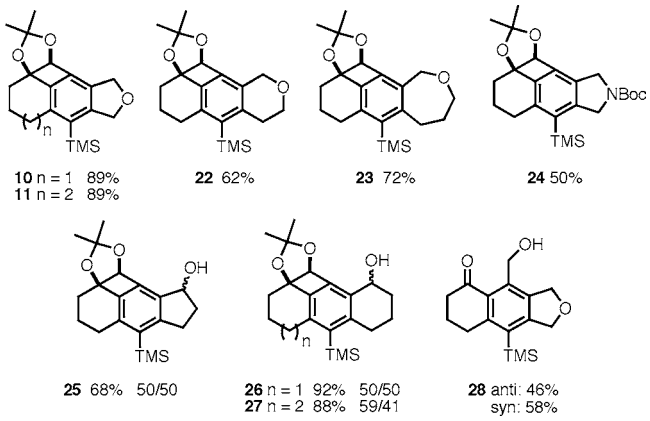
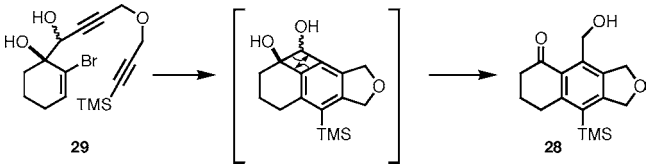


Figure 1. Synthesized compounds.

As indicated in Scheme 4, when the unprotected anti and syn diols **29** were used, the reaction resulted in the ring opening of the strained cyclobutanediol to give compound **28**, in 46 and 58% yield, respectively, from the corresponding anti and syn diastereomers.

Scheme 4. Cyclobutanediol Ring Opening



The starting enediynes **1**−**8** and **35**−**40** are prepared easily in relatively good yields from the protected diols **30** and **31**[4a,8] in a sequence of 2−5 steps (Scheme 5). After removal of the trimethylsilyl group with K_2CO_3/MeOH, the free alkyne was metalated with *n*-butyllithium in THF at −78 °C followed by addition of different aldehydes (paraformaldehyde, **41** and **42**).

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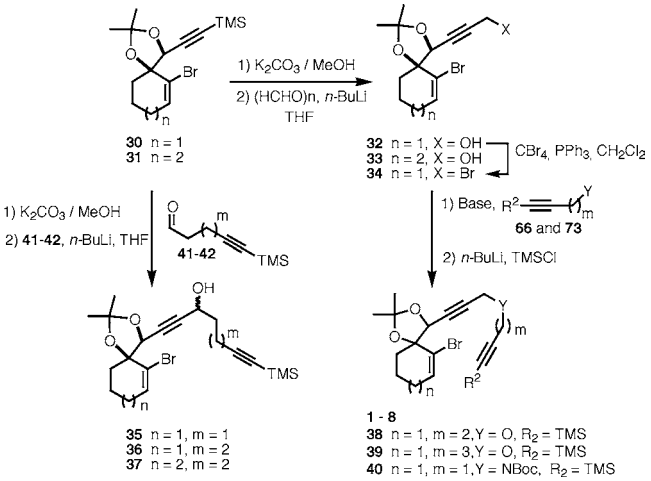
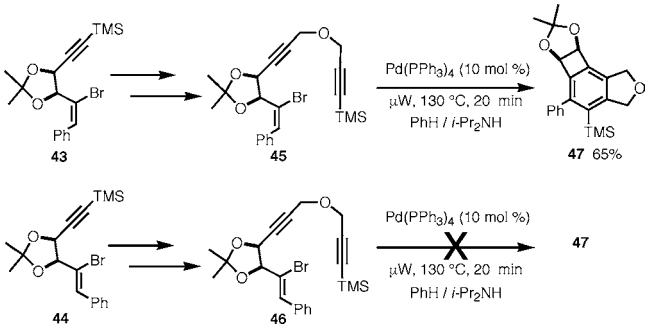
Scheme 5. Substrate Synthesis



The starting enediynes **35**−**37** are obtained from compounds **30** and **31** by desilylation and reaction with aldehyde **41** and **42**. Propargylic alcohols **32** and **33** were isolated in 87 and 73% yield, respectively. Intermediate **32** was transformed into the propargylic bromine in the presence of CBr_4/PPh_3 in 82% yield. The desired enediynes **1**−**8** and **38**−**40** were obtained from compounds **32**−**34** through a Williamson etherification.

As illustrated in Scheme 6, identical conditions were

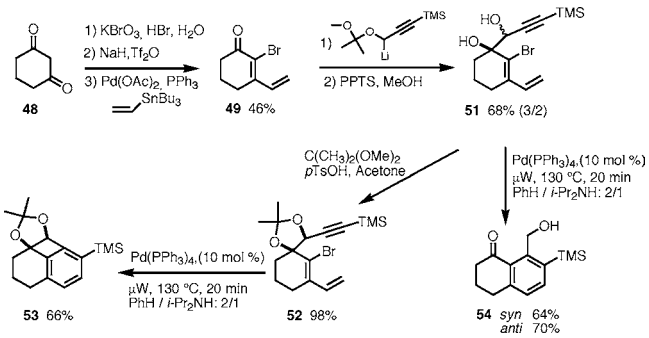
Scheme 6. Acyclic Compound Reactions



applied successfully to the corresponding acyclic *cis*-vinyl bromide **45** to give the aromatic tricyclic compounds **47** in 65% yield. When the reaction was carried out on the trans derivative **46**, no trace of cyclized product **47** was observed; the starting material was mostly recovered. Compounds **45** and **46** were prepared from **43**[4d] and **44**[4d] with the same reaction steps as described in Scheme 5 for **1**−**8**.

To generate other types of aromatic compounds by a complementary strategy, we considered the use of bromodienynes **51** and **52**. Indeed, a sequence of a 4-*exo*-dig cyclocarbopalladation, 6π electrocyclisation, or a Heck-type addition and dehydropalladation elimination should give the corresponding aromatic compounds (Scheme 7). Bromodienynes were prepared in 4 steps from commercially available cyclohexane-1,3-dione **48**.

Scheme 7. Related Strategy



After bromination, formation of the enol ether with NaH in THF, and reaction with triflic anhydride,[9] the resulting triflate was subjected to a Stille cross coupling with the vinyltributylstannane to afford compounds **49**.[10] Anti and syn diol **51** were prepared by addition of a suitable protected metalated propargylic alcohol on bromocycloalkenones followed by deprotection and chromatographic separation of the two anti and syn diastereomers.[4] The cascade was realized with the same conditions described earlier, and aromatic compound **54** was obtained. In these cases, the formation of the aromatic derivatives were followed by the opening of the cyclobutanediol moiety, and ketone **54** was isolated in 64 and 70% yields. When **51** was protected as a dioxolane, the cyclocarbopalladation of **52** produced compound **53** in 66% yield.

In conclusion, we have described a reaction cascade that produces highly functionalized, strained polycyclic aromatic compounds through a 4-*exo*-dig cyclocarbopalladation. The reaction proved to be general, avoiding the use of trialkylstannylated reagents, and will be applied on more sophisticated systems, which will be published in the near future.

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

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