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An Arylative Ring Expansion Cascade of Fused Cyclobutenes via Short-Lived Intermediates with Planar Chirality

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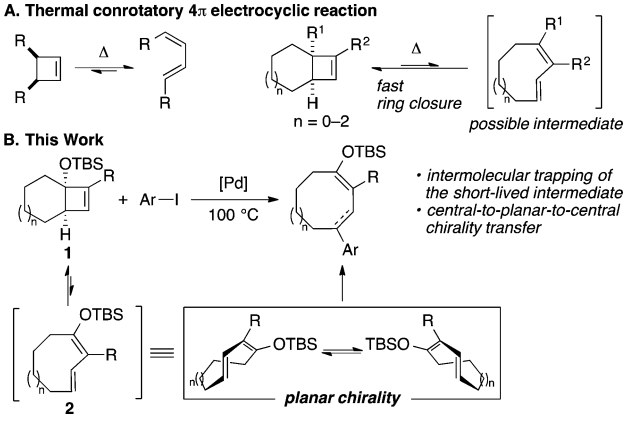
Supporting Information

ABSTRACT: An arylative ring expansion cascade has been developed for the synthesis of medium-sized carbocycles from fused cyclobutenes. This reaction proceeds through a short-lived *cis,trans*-cycloalkadiene intermediate that is formed by thermal 4π electrocyclic ring opening. Chirality transfer experiments provide direct evidence for the transient generation of the intermediate.

Medium-sized rings form the core skeletons of many natural products. Despite their importance, the synthesis of this class of compounds is a long-standing challenge in organic chemistry.[1] Intramolecular cyclization for the construction of medium-sized rings is generally difficult because of the large entropic and enthalpic costs.[2] An alternative strategy is ring expansion of fused bicyclic units. The main advantage of this approach is that it does not require high dilution or slow addition conditions, which are generally employed to prevent undesired dimerization during the cyclization process.

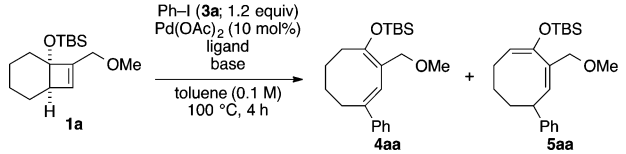
The thermal 4π electrocyclic reaction of *syn*-3,4-disubstituted cyclobutenes proceeds in a stereospecific conrotatory manner to give *cis,trans*-1,3-butadienes (Scheme 1A).[3] The thermal ring opening of cis-fused cyclobutenes could therefore generate *cis,trans*-cycloalkadienes. It has been reported that nonsubstituted bicyclo[4.2.0]octene can undergo thermal ring opening at 110 °C to give *cis,trans*-cyclooctadiene, but this compound could not be isolated because of a rapid reverse reaction to the starting material.[4] Clark and Untch[5] reported that the thermal ring opening of a substituted bicyclo[6.2.0]decene proceeded at room temperature to give a 10-membered carbocycle, whereas the use of smaller bicyclo[*n*.2.0] ring systems (n = 3−5) did not result in any of the ring-opened products, even at temperatures up to 200 °C. The authors went on to suggest that the formation of medium-sized rings containing a trans double bond would be impossible because of their severe strain. Despite this assertion, we believe that *cis,trans*-cycloalkadienes could potentially be generated as short-lived intermediates, even from substituted bicyclic compounds.[6,7] Krenske, Houk, and Hsung recently provided computational evidence to support the formation of such transient intermediates in the thermal rearrangements of fused cyclobutenes.[6] We envisioned that intermolecular trapping of the short-lived intermediate **2** using a palladium catalyst would afford medium-sized carbocycles (Scheme 1B). Notably, our attention was directed toward the possibility of chirality transfer through the inherent planar chirality of **2**, which could provide direct experimental evidence for the formation of this transient intermediate.

Scheme 1. *cis,trans*-Cycloalkadienes as Possible Intermediates for the Synthesis of Medium-Sized Carbocycles



The trapping of **2** was initially attempted using an intermolecular Heck reaction (Table 1). When **1a** was treated with iodobenzene (**3a**) in toluene at 100 °C in the presence of $Pd(OAc)_2$, PPh_3, and *N*,*N*-diisopropylethylamine (DIPEA), the *cis,cis*-cyclooctadiene **4aa** was obtained in 34% yield (entry 1).[8] When Cs_2CO_3 was used, formation of the olefinic isomer **5aa**

Table 1. Selected Optimization of the 4π Electrocyclic Ring Opening−Heck Arylation Cascade[a]



entry	base (equiv)	ligand (mol %)	yield (%)[b]	4aa/5aa[c]
1	DIPEA (2.0)	PPh_3 (20)	34	>20:1
2	Cs_2CO_3 (2.0)	PPh_3 (20)	30	9:1
3	AgOAc (2.0)	PPh_3 (20)	83	8:1
4	Ag_2CO_3 (1.0)	PPh_3 (20)	90	14:1
5	Ag_2CO_3 (1.0)	PCy_3 (20)	64	1:2
6	Ag_2CO_3 (1.0)	dppb (10)	61	1:1

[a]The reactions were run on a 0.2 mmol scale. [b]Combined isolated yields. [c]Determined by ^{1}H NMR analysis of the isolated products.

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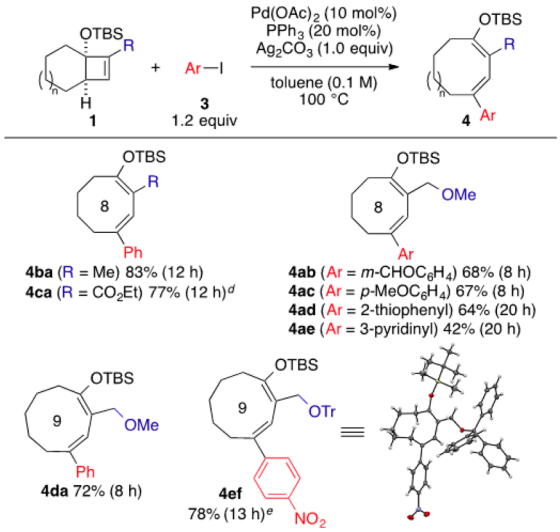
was observed (entry 2). The use of silver salts had a positive impact on the yield of **4aa**, with Ag_2CO_3 being the most suitable (entries 3 and 4). No improvements were observed in the yield or selectivity using other ligands (entries 5 and 6). It is noteworthy that no ring-opening compounds were obtained when **1a** was heated under the same conditions in the absence of the palladium catalyst.

With the optimized conditions in hand, we investigated the substrate scope of the ring expansion−arylation cascade (Scheme 2). The reaction of cyclobutenes bearing an alkyl or

Scheme 2. Substrate Scope of the 4π Electrocyclic Ring Opening−Heck Arylation Cascade[a,b,c]



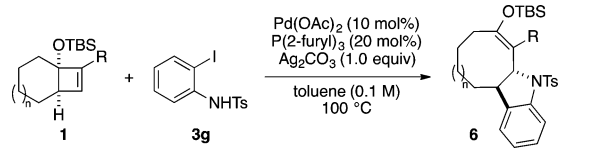
[a]The reactions were run on a 0.2 mmol scale, unless noted otherwise. [b]Isolated yields are shown. [c]**4**/**5** > 20:1, unless noted otherwise. [d]**4ca**/**5ca** = 16:1. [e]The reaction was run on a 1.2 mmol scale.

alkoxycarbonyl group proceeded smoothly (**4ba** and **4ca**). The use of an aryl iodide bearing an electron-withdrawing group (**4ab**) or an electron-donating group (**4ac**) was well-tolerated. Heteroaryl iodides, including 2-iodothiophene and 3-iodopyridine, also reacted smoothly (**4ad** and **4ae**). Pleasingly, this reaction was also successfully applied to seven-membered-ring-fused cyclobutenes to afford the corresponding cyclononadienes (**4da** and **4ef**). The structure of **4ef** was unambiguously determined by X-ray crystallographic analysis.

We then investigated the use of *N*-tosyl-2-iodoaniline (**3g**) as the aryl iodide to obtain medium-ring-fused *trans*-indolines **6** (Table 2). After screening of several ligands, P(2-furyl)$_3$ was identified as the most appropriate ligand for this transformation (see the Supporting Information). The reaction of six-membered-ring-fused cyclobutenes provided eight-membered-ring-fused indolines as single diastereomers (entries 1 and 2). Using **1a** led to the simultaneous elimination of the methoxy group to give **6a** in 54% yield (entry 3). The use of the seven-membered-ring-fused cyclobutenes **1g** and **1h** furnished the corresponding nine-membered-ring-fused indolines (entries 4 and 5). The reaction of tricyclic cyclobutenes also proceeded smoothly to afford the corresponding products with increased reaction rates (entries 6−8).

Our proposed mechanism for the formation of **6** is shown in Scheme 3. Oxidative addition of Pd^0 to **3g** in the presence of Ag_2CO_3 would generate the cationic aryl Pd species **I**. This Pd species would then undergo a syn insertion into the trans olefin

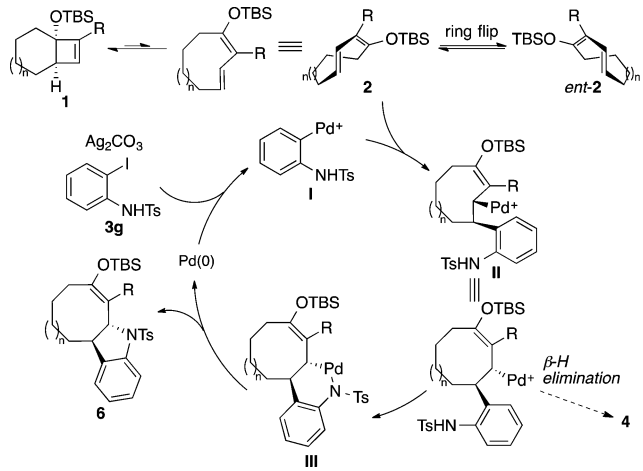
Table 2. Substrate Scope for the Synthesis of Medium-Ring-Fused Indolines 6[a]



entry	substrate **1**	product **6**	time	yield (%)[b]
1	**1c** (R = CO_2Et)	**6c**	4 h	75
2	**1f** (R = CH_2NHNs)	**6f**	12 h	53
3	**1a**	**6a**	12 h	54
4	**1g** (R = CO_2Et)	**6g**	4 h	80
5	**1h** (R = CH_2NHNs)	**6h**	6 h	64
6	**1i** (R = CO_2Et, X = CH_2)	**6i**	10 min	74
7	**1j** (R = Me, X = CH_2)	**6j**	2 h	45[c]
8	**1k** (R = CO_2Et, X = O)	**6k**	30 min	79

[a]The reactions were run on a 0.2 mmol scale, unless noted otherwise. [b]Isolated yields. [c]The reaction was run on a 0.1 mmol scale.

Scheme 3. Working Mechanistic Hypothesis for the Synthesis of Medium-Ring-Fused Indoline 6 with Chirality Transfer



of **2**, which would be generated as a transient intermediate by the thermal 4π electrocyclic reaction of **1**. The resulting Pd^{II} complex **II** would be converted to the six-membered palladacycle **III** at a higher rate than the β-hydride elimination to give **4**.[9] Subsequent reductive elimination from **III** would give **6**.[10] We envisaged that this reaction would result in chirality transfer through the planar chirality of **2**. Certain medium-sized-ring *trans*-cycloalkenes have been reported to possess planar chirality. As a representative example, *trans*-

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cyclooctene exhibits stable planar chirality at ambient temperature because of its highly rigid structure.[11] For chirality transfer to occur, the addition of **2** to **I** must occur at a higher rate than the racemization of **2** by ring flip.

The chirality transfer was examined using optically pure substrates (Table 3), which were prepared by preparative chiral

Table 3. Chirality Transfer in the Synthesis of Indoline 6 using Enantiopure Cyclobutenes[a]

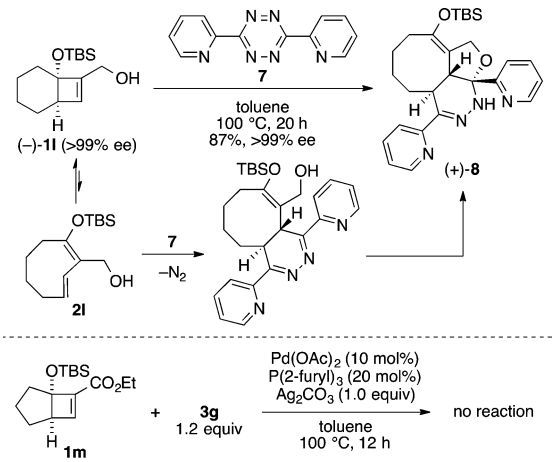
entry	1	T (°C)	time	yield of 6 (%)[b]	ee of 6 (%)[c]
1	(−)-**1c**	100	4 h	79 ((+)-**6c**)	>99
2	(−)-**1g**	100	4 h	81 ((±)-**6g**)	0
3	(−)-**1i**	100	10 min	73 ((+)-**6i**)	74
4	(−)-**1i**	50	24 h	72 ((+)-**6i**)	85
5	(−)-**1k**	100	30 min	78 ((+)-**6k**)	84
6	(−)-**1k**	50	24 h	78 ((+)-**6k**)	94

[a]The reactions were run on a 0.1 mmol scale using enantiopure substrate **1** (>99% ee), **3g** (1.2 equiv), $Pd(OAc)_2$ (10 mol %), P(2-furyl)$_3$ (20 mol %), and Ag_2CO_3 (1.0 equiv). [b]Isolated yields. [c]Determined by chiral HPLC.

HPLC.[12] When (−)-**1c** was subjected to the reaction at 100 °C, (+)-**6c** was obtained without any loss of optical purity (entry 1). The absolute configuration of (+)-**6c** was determined by X-ray analysis, and the stereochemical outcome was found to be in reasonable agreement with our hypothesis (Scheme 3). When (−)-**1c** was heated in toluene at 100 °C for 12 h in the absence of the palladium catalyst, there was no decrease in the enantiomeric purity of the recovered **1c**, which suggested that the eight-membered transient intermediate has a high energy barrier to racemization. In sharp contrast, the use of seven-membered-ring-fused (−)-**1g** provided **6g** as a racemic mixture (entry 2). Furthermore, complete racemization was observed during the formation of **6g** even at 60 °C. The dramatic difference in the extent of the chirality transfer reflects the fact that the increased ring size significantly facilitates the racemization by ring flip.[13] Interestingly, the chirality was retained in the reaction of the seven-membered-ring-fused tricyclic cyclobutene (−)-**1i**, which gave (+)-**6i** with 74% ee (entry 3). The introduction of a benzene ring could lead to an increase of the stereochemical stability of the *cis,trans*-cyclononadiene intermediate.[14] When the reaction was conducted at 50 °C for 24 h, the enantiomeric excess of (+)-**6i** improved to 85% ee (entry 4). Notably, the oxygen-containing substrate (−)-**1k** was converted to (+)-**6k** with a higher degree of chirality transfer than in the case of **1i** (entries 3 and 4 vs entries 5 and 6). The stereochemical stability of **2** may be enhanced by the replacement of the methylene group with an oxygen atom because of the shorter length of the C−O bond compared with the C−C bond.[15] The results of these chirality transfer experiments therefore provide direct evidence for the transient generation of **2**. Consequently, these reactions can be classified as a rare example of the memory of chirality involving transient planar-chiral intermediates.[16,17] Further research toward the development of this phenomenon could therefore make a significant contribution to the area of asymmetric synthesis.

To rule out the possibility that the observed chirality transfer occurred through a chiral palladium species, (−)-**1l** was treated with a tetrazine, which is known to be very effective in cycloaddition with *trans*-cyclooctene derivatives (Scheme 4).[18] When (−)-**1l** and tetrazine **7** were heated in toluene at 100 °C,

Scheme 4. Experimental Support for the Formation of the Transient Intermediate 2



the transient intermediate was trapped to form adduct **8** in 87% yield. Most notably, this reaction resulted in complete chirality transfer, which confirmed that the chirality transfer in the synthesis of indoline **6** occurred via a planar-chiral intermediate.[19] The intermediacy of **2** was further supported by the inert behavior of bicyclo[3.2.0]heptane **1m**, which can be rationalized by assuming that the transient *cis,trans*-cycloheptadiene is highly strained because of the smaller ring size.[6b,20]

In summary, we have developed a ring-expansion cascade of fused cyclobutenes via short-lived *cis,trans*-cycloalkadiene intermediates. Chirality transfer was observed in the synthesis of indolines, and the extent of this transfer was highly dependent on the ring size of the transient intermediate and increased by the introduction of a benzene ring or an oxygen atom. Further work is currently underway in our laboratory to explore the novel reactions of fused cyclobutenes and develop the memory of chirality through transient planar chirality.

■ ASSOCIATED CONTENT

Supporting Information

Spectral data for all of the new compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b06576.

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Notes

The authors declare no competing financial interest.

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