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Synthesis of Helicenes Utilizing Palladium-Catalyzed Double C−H Arylation Reaction

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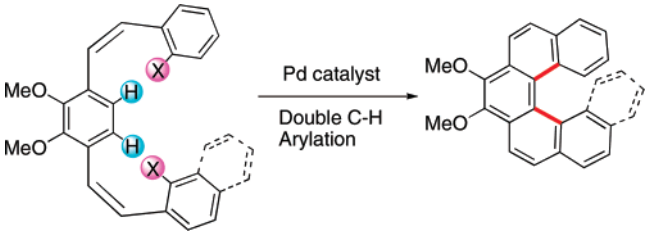

[5]- and [6]helicenes were synthesized in moderate to good yields from *Z*,*Z*-bis(bromostilbene)s by palladium-catalyzed double C−H arylation reaction. This method can be applied to the syntheses of helicenes possessing electron-deficient substituents.

Helicenes possessing inherent helical chiralities have been attracting increasing attention owing to their extraordinary optical[1] and electronic[2] properties. Their ability to bind to specific DNA structures has been demonstrated.[3] In addition to the previously reported photocyclization reaction,[4] new methodologies,[5,6] including Diels−Alder cycloaddition,[7] carbenoid insertion,[8] and [2 + 2 + 2] cycloisomerization,[9] have been developed. Tandem radical cyclization reported by Harrowven et al. is a practical and efficient method for the synthesis of helicenes.[10] However, there is still considerable room for the development of helicene synthesis. As part of our program aimed at establishing efficient methods for the synthesis of helical molecules, we have developed an alternative approach to helicene synthesis, which involves palladium-catalyzed double C−H arylation reaction utilizing *Z*,*Z*-bis(stilbene)s.

Palladium- or rhodium-catalyzed C−H arylation is a powerful method for the synthesis of heterocycles as it eliminates the need to preactivate coupling components.[11−13] Thus, we initially examined the synthesis of 1,2-dimethoxyphenanthrene (**2**) by C−H arylation utilizing a Pd catalyst (Table 1). Iodostilbene **1**, which was prepared by conventional Wittig reaction, was treated with $PdCl_2$(dppf) and KOAc in DMSO at 90 °C (entry 1). However, the reaction proceeded slowly to give the product in 37% yield. When the reaction temperature was increased to 130 °C, the yield was improved to 55% (entry 2). Of the solvents examined, DMA was found to be the most suitable (entries 3

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TABLE 1. Synthesis of Phenanthrene by Intramolecular C−H Arylation Reaction

entry	Pd cat.	*T* (°C)	solvent	base	yield (%)
1	$PdCl_2$(dppf)	90	DMSO	KOAc	37
2	$PdCl_2$(dppf)	130	DMSO	KOAc	55
3	$PdCl_2$(dppf)	130	DMF	KOAc	51
4	$PdCl_2$(dppf)	130	DMA	KOAc	62
5	$PdCl_2(PhCN)_2$	130	DMA	KOAc	51
6	$Pd(OAc)_2$	130	DMA	KOAc	68
7	$Pd(OAc)_2$	130	DMA	K_2CO_3	99

and 4). We next surveyed palladium catalysts (entries 5 and 6). It was found that $Pd(OAc)_2$ is the most suitable for this reaction (entry 6). Finally, when the base was changed from KOAc to K_2CO_3,[13i,j] the reaction was dramatically improved to give the desired phenanthrene **2** in quantitative yield (entry 7).

With the optimized conditions for the C−H arylation of iodostilbene in hand, we next examined the utility of the double C−H arylation of bis(iodostilbene) for the efficient synthesis of [5]helicene. Initially, we applied the optimized conditions mentioned above to the synthesis of [5]helicene by the double C−H arylation reaction. However, the major product was phenanthrene derivative **5**, which was formed by the single C−H arylation reaction of each compound (Table 2, entry 1). To improve the yield of [5]helicene, we examined the effects of such additives as ammonium salts or silver salts (entries 2−5). *n*-Bu_4NCl slightly improved the yield of desired [5]helicene **4** (entry 2). On the other hand, Ag_2CO_3 gave the best result among the additives examined (entry 5). For further improvement, the ligand effect was examined. Bulky and electron-rich ligands, such as P^tBu_3·HBF_4, PCy_2(2-MePh), and PCy_2Ph, were not suitable for this reaction (entries 6−8). In contrast, PCy_3, particularly air-stable PCy_3·HBF_4, improved the yield to 48% (entries 9 and 10).[14] Since the yield of **4** was decreased to 14% when the reaction was performed without Ag_2CO_3, it was confirmed that the silver salt was crucial for this reaction (entry 11). Ligands smaller than PCy_3, such as $PCy_2{}^iPr$ and P^iPr_3, gave phenanthrene **5** in good yield but not the desired [5]helicene (entries 12 and 13). Commercially available Buchwald ligands and *N*-heterocarbene ligands were also examined, but they were not effective for the reaction.

We also examined the effect of the halogen group (Table 3). When the halogen group of **3** was changed from iodide to bromide, the yield of **4** was improved to 75% (entry 2). However, when chloride was used, the reaction did not proceed and the starting material was recovered (entry 3). Finally, we examined the substrate for the synthesis of helicene by the double C−H arylation reaction (Scheme 1). When the reaction was performed using related electron-deficient substrates **9a** and **9b**, 3,12-difluoro-7,8-dimethoxy[5]helicene (**10a)** and 3-fluoro-7,8-dimethoxy[5]helicene (**10b)** were obtained in good to moderate yields. However, when **9c**, which has an electron-donating methoxy group, was used, the reaction gave a complex mixture without the desired helicene **10c**.

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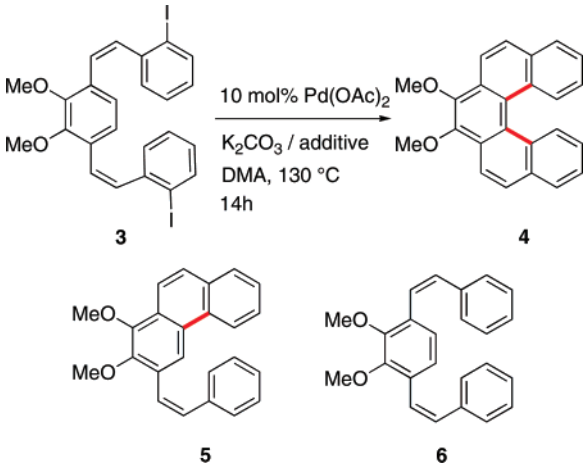
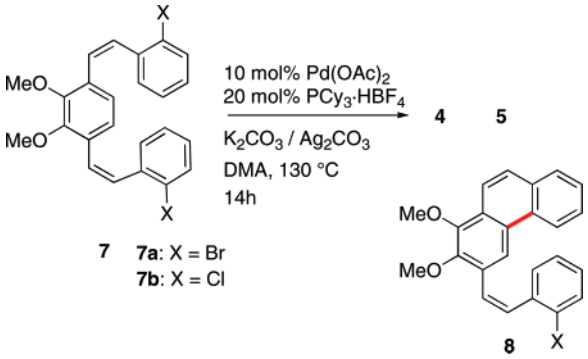
TABLE 2. Synthesis of [5]Helicene by Double C−H Arylation Reaction



entry	additive (equiv)	ligand (20 mol %)	**4** (%)	**5** (%)	**6** (%)
1			6	45	35
2	*n*-Bu_4NCl (1.0)		13	39	38
3	Et_4NCl (1.0)			60	27
4	AgOTf (1.0)			61	13
5	Ag_2CO_3 (0.5)		20	37	39
6	Ag_2CO_3 (0.5)	P^tBu_3·HBF_4		67	33
7	Ag_2CO_3 (0.5)	PCy_2(2-MePh)			
8	Ag_2CO_3 (0.5)	PCy_2Ph		100	
9	Ag_2CO_3 (0.5)	PCy_3	27	26	9
10	Ag_2CO_3 (0.5)	PCy_3·HBF_4	48	35	
11		PCy_3·HBF_4	14	14	
12	Ag_2CO_3 (0.5)	$PCy_2{}^iPr$		91	9
13	Ag_2CO_3 (0.5)	P^iPr_3		85	15

TABLE 3. Effect of Halogen Group

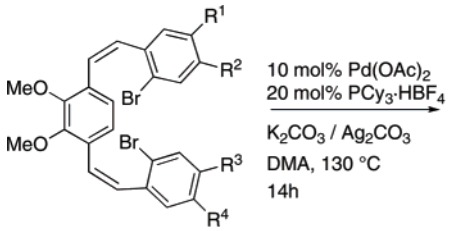


entry	X	compd	**4** (%)	**5** (%)	**8** (%)
1	I	**3**	48	35	
2	Br	**7a**	75	15	
3	Cl	**7b**			8

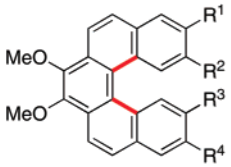
These results sharply contrasted that of tandem radical cyclization[9] in which the yield was improved by the introduction of an electron-donating methoxy group. Thus, the palladium-catalyzed double C−H arylation reaction can be used to complement the synthesis of electron-deficient helicenes.

We next examined the synthesis of [6]helicene (Scheme 2). Despite the sterically hindered substrate, we were able to synthesize desired [6]helicene **12** in 30% yield. Other products were complex mixtures of debrominated products and the product formed by single C−H arylation. We also examined

SCHEME 1. Synthesis of [5]Helicene Derivatives

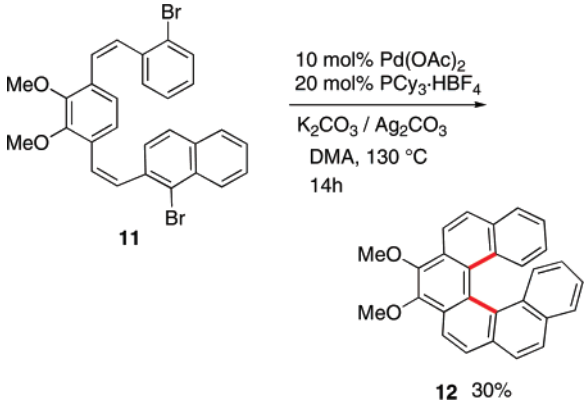


9 **9a**: R^1, R^4 = F, R^2, R^3 = H
9b: R^1 = F, R^2, R^3, R^4 = H
9c: R^1, R^4 = OMe, R^2, R^3 = H



10 **10a**: R^1, R^4 = F, R^2, R^3 = H 86%
10b: R^1 = F, R^2, R^3, R^4 = H 45%
10c: R^1, R^4 = OMe, R^2, R^3 = H –

SCHEME 2. Synthesis of [6]Helicene by Double C−H Arylation Reaction



11

12 30%

the synthesis of [7]helicene; however, the desired product could not be obtained.

In conclusion, we have developed a palladium-catalyzed double C−H arylation reaction for the synthesis of [5] or [6] helicenes. This is a good alternative to the efficient synthesis of helicenes by radical cyclization, particularly the synthesis of electron-deficient helicenes. The advantages of the double C−H arylation reaction could be extended to the catalytic asymmetric synthesis of optically active helicenes using a suitable combination of transition metals and chiral ligands. Investigations are underway in this laboratory.

Experimental Section

General Procedure for the Synthesis of *Z*,*Z*-Bis(bromostilbene). 2-Bromobenzyl bromide phosphonium salt (5.7 mmol) was treated with potassium *tert*-butoxide (5.9 mmol) in THF (20 mL)/H_2O (2 mL) at 0 °C and stirred for 15 min. 2,3-Dimethoxy-1,4-dicarbaldehyde (2.6 mmol) was added, and the mixture was stirred for 30 min at rt. The resulting mixture was extracted with EtOAc and washed with brine. The crude product was purified by gel permeation chromatography (70−80%). Compound **9a**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 3.86 (6H, s), 6.48 (2H, s), 6.61 (2H, d, J = 12.0 Hz), 6.74−6.84 (6H, m), 7.45−7.49 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 60.8, 116.0, 117.1, 117.4, 124.4, 127.2, 129.3, 130.2, 133.7, 133.8, 151.4, 162.6; IR ($CHCl_3$) 3356, 3157, 2994, 2937, 1601, 1573, 1459 cm^{-1}; MS (70 eV) *m*/*z* 536 (100), 534 (M^+, 49); HRMS calcd for $C_{24}H_{18}O_2F_2Br_2$ 533.9642, found 533.9640.

General Procedure for Double C−H Arylation Reaction. *Z*,*Z*-Bis(bromostilbene) (0.20 mmol), $Pd(OAc)_2$ (0.020 mmol, 10 mol %), K_2CO_3 (0.40 mmol, 2.0 equiv), Ag_2CO_3 (0.10 mmol, 0.5 equiv), PCy_3·HBF_4 (0.04 mmol, 0.2 equiv), and DMA (2.0 mL) were mixed in a Schlenk tube and stirred for 14 h at 130 °C under argon. The resulting mixture was purified by silica gel chromatography (hexane/EtOAc = 9/1) to give the product. Compound **10a**: ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C) δ 4.13 (6H, s), 7.01 (2H, m), 7.55 (2H, dd, J = 9.0, 3.0 Hz), 7.88 (2H, d, J = 9.0 Hz), 8.30 (2H, d, J = 9.0 Hz), 8.33−8.36 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C) δ 61.2, 111.3, 111.5, 113.9, 114.2, 121.1, 124.2, 127.0, 127.1, 131.0, 131.1, 133.5; IR ($CHCl_3$) 3655, 3361, 3158, 2946, 2846, 1800, 1618, 1565, 1462 cm^{-1}; MS (70 eV) *m*/*z* 374 (M^+, 100), 359 (47); HRMS calcd for $C_{24}H_{16}F_2O_2$, 374.1118, found 374.1118.

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Supporting Information Available: The characterization of compounds and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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