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Palladium-Catalyzed Allenylation/Intramolecular Diels–Alder Reaction of Furans with Propargyl Carboxylates for the Synthesis of Polycyclic Compounds

Chengyu Wang,[a] Lingkai Kong,[a] Yanli Li,[a] and Yanzhong Li*[a]

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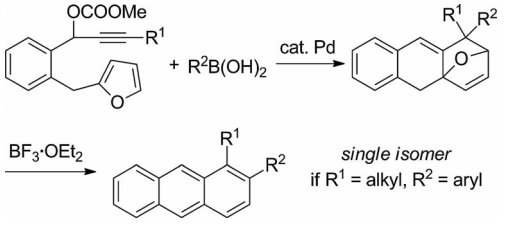
A highly efficient palladium-catalyzed cascade reaction of propargyl carboxylates bearing a furanyl group with organoborons was developed. This methodology offers rapid access to polycyclic Diels–Alder cycloadducts in good to high yields. The thus-formed oxygen-bridged products were further converted into anthracene derivatives in a chemoselective manner under mild conditions.

Introduction

The Diels–Alder reaction of furans is of great importance in organic synthesis.[1] The resulting oxygen-bridged norbornenes or norbornadienes are valuable precursors to functionalized polycyclic compounds.[2] The intramolecular Diels–Alder reaction of furans[3] is particularly attractive because of its many benefits, including the ability to construct two or more rings in one step, rate enhancement, and better defined regioselectivity. In these reactions, furans participate as diene components, and a variety of dienophiles such as alkenes,[4] alkynes,[5] and allenes[6] are compatible. However, if alkynes are employed as dienophiles, only those with electron-withdrawing groups at the terminal sp carbon atom or terminal alkynes[7] work well. Very few studies with alkynes bearing normal alkyl or aryl groups at their terminus have been reported[8] to the best of our knowledge. This has greatly curtailed the scope and potential of this methodology in synthetic organic chemistry. This is likely due to the low reactivity of the unactivated alkynes. In contrast, allenes are much more reactive than alkynes as dienophiles.[3a] It was documented that Pd^0-catalyzed cross-coupling reactions of propargylic compounds with organoborons afford allene derivatives.[9] We envisioned that propargyl compounds, such as propargyl carbonates, might be used as unactivated alkyne components to initiate the intramolecular Diels–Alder reaction of furans by proper choice of catalysts and organoborons. Herein, we report a novel Pd^0-catalyzed intramolecular Diels–Alder reaction of furans with propargyl carboxylates in the presence of organoborons to afford oxygen-bridged polycyclic compounds in high yields, and we also report the further transformation of the products into anthracene derivatives in a chemoselective manner (Scheme 1).



Scheme 1. Palladium-catalyzed cascade reactions for the synthesis of polycyclic compounds.

Results and Discussion

The requisite propargylic carbonates with a furyl group, that is, **1**, were readily prepared from the reaction of 2-(furan-2-ylmethyl)benzaldehyde with terminal alkynes followed by esterification with methyl chloroformate. First, the reaction of propargyl carbonate **1a** possessing a phenyl group on the triple bond with phenylboronic acid (**2a**) was performed by using $Pd(OAc)_2$ (5 mol-%) as the catalyst and K_2CO_3 (2 equiv.) as the base in THF at 100 °C. However, desired cycloadduct **3a** was not detected (Table 1, entry 1). By changing the catalyst to $PdCl_2(PPh_3)_2$, **3a** was obtained in 52% yield (Table 1, entry 2). $Pd(PPh_3)_4$ afforded a higher yield of **3a** (Table 1, entry 4). If the amount of **2a** was increased to 4.0 equiv., the yield of **3a** increased to 66% (Table 1, entry 5). Interestingly, if Cs_2CO_3 was used instead of K_2CO_3, the yield of **3a** increased to 74% (Table 1, entry 6). If the reaction was performed at 80 °C, **3a** was produced in 52% yield (Table 1, entry 7). Lowering the catalyst loading to 2 mol-% gave 72% yield of the adduct with

[a] Shanghai Key Laboratory of Green Chemistry and Chemical Processes, Department of Chemistry, East China Normal University,
500 Dongchuan Road, Shanghai 200241, P. R. China
E-mail: yzli@chem.ecnu.edu.cn
http://www.chem.ecnu.edu.cn/

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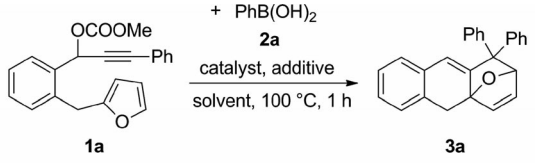
prolonged reaction time (Table 1, entry 8). Other bases such as Et_3N, NaOMe, and KO*t*Bu did not give better results than those obtained with Cs_2CO_3 (Table 1, entries 9–11). By changing the solvent to EtOH or DMF, **3a** was produced in a relatively low yield (Table 1, entries 12 and 13). Therefore, the optimized reaction conditions involved the use of $Pd(PPh_3)_4$ (5 mol-%) as the catalyst, Cs_2CO_3 (2.0 equiv.) as the base, and THF as the solvent at 100 °C.

Table 1. Optimization of the reaction conditions for the synthesis of **3a**.



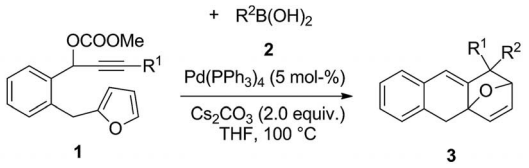
1a **3a**

Entry	Catalyst (mol-%)	Additive (equiv.)	Solvent	Yield [%][a]
1	$Pd(OAc)_2$ (5)	K_2CO_3 (2.0)	THF	–
2	$Pd(PPh_3)_2Cl_2$ (5)	K_2CO_3 (2.0)	THF	52
3	$Pd_2(dba)_3$ (5)	K_2CO_3 (2.0)	THF	–
4	$Pd(PPh_3)_4$ (5)	K_2CO_3 (2.0)	THF	63
5	$Pd(PPh_3)_4$ (5)	K_2CO_3 (2.0)	THF	66[b]
6	$Pd(PPh_3)_4$ (5)	Cs_2CO_3 (2.0)	THF	74
7	$Pd(PPh_3)_4$ (5)	Cs_2CO_3 (2.0)	THF	52[c]
8	$Pd(PPh_3)_4$ (2)	Cs_2CO_3 (2.0)	THF	72[d]
9	$Pd(PPh_3)_4$ (5)	Et_3N (2.0)	THF	55
10	$Pd(PPh_3)_4$ (5)	NaOMe (2.0)	THF	trace[e]
11	$Pd(PPh_3)_4$ (5)	KO*t*Bu (2.0)	THF	28[d]
12	$Pd(PPh_3)_4$ (5)	Cs_2CO_3 (2.0)	CH_3CH_2OH	51
13	$Pd(PPh_3)_4$ (5)	Cs_2CO_3 (2.0)	DMF	63

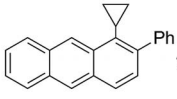
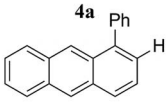
[a] Yield of isolated products. Unless otherwise noted, all reactions were performed in screw-capped tubes by using $PhB(OH)_2$ (2.0 equiv.). dba = dibenzylideneacetone. [b] $PhB(OH)_2$ (4.0 equiv.). [c] The reaction was performed at 80 °C. [d] The reaction time was 2 h. [e] The reaction time was 14 h.

With the optimized reaction conditions in hand, we next examined the substrate scope of this catalytic method for the synthesis of Diels–Alder cycloadducts by using a variety of propargylic carbonates and boronic acids; the results are shown in Table 2. We first investigated the electronic effects of the aromatic substituents on the triple bond. It was found that substrate **1b** possessing an electron-withdrawing (–Cl) aryl group reacted with **2a** and (4-chlorophenyl)-boronic acid (**2b**) to afford corresponding product **3b** and **3c** in 54 and 78% yield, respectively (Table 2, entries 1 and 2). Substrate **1c** with a 4-(trifluoromethyl)phenyl group reacted with [4-(trifluoromethyl)phenyl]boronic acid (**2c**) to produce **3d** in 77% yield (Table 2, entry 3). Substrate **1d** containing an electron-donating (–OMe) aryl group reacted with **2a** and (4-methoxylphenyl)boronic acid (**2d**) to give desired cycloadducts **3e** and **3f** in 72 and 63% yield, respectively (Table 2, entries 4 and 5). The reaction of **1e** bearing a 3,5-dimethoxylphenyl group with **2a** and (3,5-dimethoxylphenyl)boronic acid (**2e**) gave desired products **3g** and **3h** in good yields (Table 2, entries 6 and 7). The structure of **3h** was further confirmed by X-ray crystallographic analysis.[10] The substituents on the triple bond could also be alkyl groups; *n*-butyl-substituted **1f** furnished **3i** in 78% yield (Table 2, entry 8). Cyclopropyl-substituted **1g** and terminal alkyne **1h** also reacted smoothly with **2a** to produce the Diels–Alder cycloadducts. However, these compounds were not stable. They were further treated with $BF_3{\cdot}OEt_2$ and converted into anthracene derivatives **4a** and **4b**,

Table 2. Synthesis of various of polycyclic compounds.



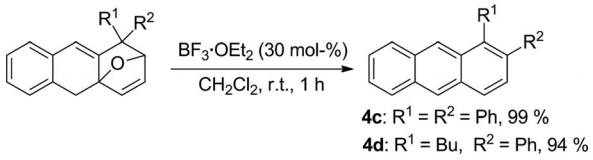
1 **3**

Entry	R^1	R^2	Product	Yield [%] (*dr*)[a]
1	4-ClC_6H_4 (**1b**)	Ph (**2a**)	**3b**	54 (1:1)
2	4-ClC_6H_4 (**1b**)	4-ClC_6H_4 (**2b**)	**3c**	78
3	4-$CF_3C_6H_4$ (**1c**)	4-$CF_3C_6H_4$ (**2c**)	**3d**	77
4	4-$MeOC_6H_4$ (**1d**)	Ph (**2a**)	**3e**	72 (1:1)
5	4-$MeOC_6H_4$ (**1d**)	4-$MeOC_6H_4$ (**2d**)	**3f**	63
6	3,5-$(MeO)_2C_6H_3$ (**1e**)	Ph (**2a**)	**3g**	68 (1:1)
7	3,5-$(MeO)_2C_6H_3$ (**1e**)	3,5-$(MeO)_2C_6H_3$ (**2e**)	**3h**	76
8	*n*Bu (**1f**)	Ph (**2a**)	**3i**	78 (1.6:1)
9	cyclopropyl (**1g**)	Ph (**2a**)	 **4a**	78[b]
10	H (**1h**)	Ph (**2a**)	 **4b**	64[b]
11	Ph (**1a**)	4-ClC_6H_4 (**2b**)	**3b**	73 (1:1)
12	Ph (**1a**)	4-$MeOC_6H_4$ (**2d**)	**3e**	70 (1:1)
13	Ph (**1a**)	3,5-$(MeO)_2C_6H_3$ (**2e**)	**3g**	68 (1:1)
14	Ph (**1a**)	phenylethyl (**2f**)	**4b**	44[b]
15	R^3 = Me (**1i**)	Ph (**2a**)	**3j**	50
16	R^3 = 3,5-$(CF_3)_2C_6H_3$ (**1j**)	Ph (**2a**)	**3k**	58

[a] Yield of isolated products. Diastereomeric ratio is given in parentheses. Unless noted, all the reactions were performed in screw-capped tubes by using $Pd(PPh_3)_4$ (5 mol-%) and Cs_2CO_3 (2.0 equiv.) in THF at 100 °C. [b] The crude product was further treated with $BF_3{\cdot}OEt_2$ (30 mol-%) in dichloromethane.

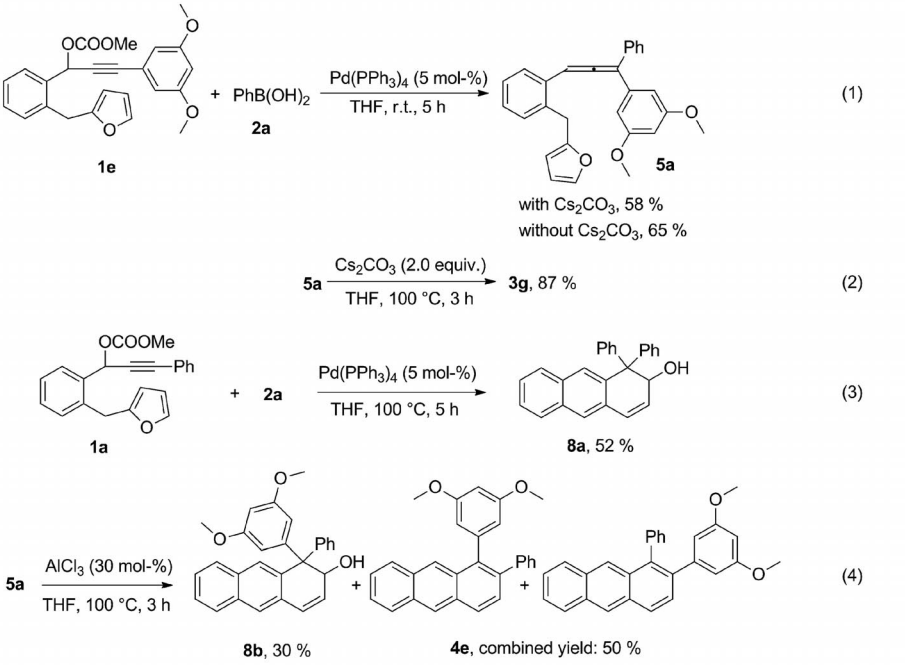
respectively (Table 2, entries 9 and 10). The structures of **4a** and **4b** were further confirmed by X-ray diffraction analysis.[10] Boronic acids both with electron-withdrawing and electron-donating aryl groups, for example, 4-chloro-substituted **2b**, 4-methoxy-substituted **2d**, and 3,5-dimethoxylphenyl-substituted **2e**, were also compatible in the reaction; they afforded corresponding cycloadducts **3b**, **3e**, and **3g** in 73, 70, and 68% yield, respectively (Table 2, entries 11–13). If alkyl-substituted boronic acid **2f** was employed in the reaction, anthracene **4b** was produced in 44% yield after further treatment with $BF_3{\cdot}OEt_2$. The phenylethyl group of the boronic acid was not incorporated in the final product; this may be due to β-hydrogen elimination of the allenyl palladium intermediate (Table 2, entry 14). To further broaden the substrate scope of this procedure, we attempted to prepare propargyl carbonates with one more substituents at the propargylic position. However, the protection of the OH group of the tertiary alcohol by using methyl chloroformate was not successful for our substrates. Then, we turned our attention to tertiary propargyl acetates. Propargyl acetate **1i** with a methyl group at the propargylic position reacted smoothly with **2a** to give desired cycloadduct **3j** in 50% yield (Table 2, entry 15). Substrate **1j** with a 3,5-ditrifluoromethylphenyl group resulted in corresponding **3k** in 58% yield (Table 2, entry 16). In these cases, one more substituents were successfully introduced into the polycyclic products.

The utility of the oxygen-bridged cycloadducts as useful synthetic intermediates was investigated by simple treatment with $BF_3{\cdot}OEt_2$, which afforded anthracene derivatives in high yields as exemplified by **4a** and **4b** (Table 2, entries 9, 10, 14). Upon treating **3a** and **3i** with $BF_3{\cdot}OEt_2$, corresponding **4c** and **4d** were obtained in 99 and 94% yield, respectively (Scheme 2). Notably, there was selective migration of the aryl group over the alkyl group during the aromatization. The structure of **4d** was further confirmed by X-ray crystallographic analysis.[10]



Scheme 2. Further conversion into anthracene derivatives.

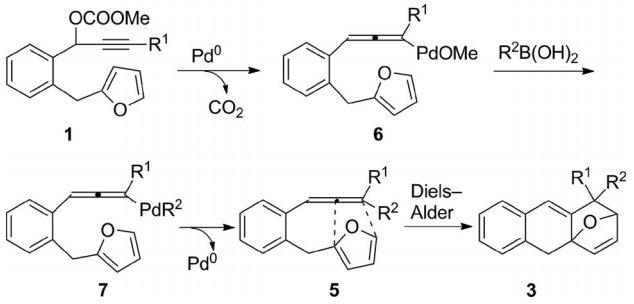
To understand the mechanism, we carefully examined the reaction of 3-(3,5-dimethoxyphenyl)-1-[2-(furan-2-ylmethyl)phenyl]prop-2-ynyl methyl carbonate (**1e**) with phenylboronic acid (**2a**) at room temperature. It was found that allenic intermediate **5a** was obtained in 58% yield in the presence of Cs_2CO_3 after 5 h, along with some of the unreacted starting materials [Scheme 3, Equation (1)]. Isolated **5a** was subjected to basic conditions to afford **3g** in 87% yield in 3 h [Scheme 3, Equation (2)]. Notably, allenic **5a** was transformed into **3g** in 45% yield without the addition of a base at 100 °C after 3 h. This indicated that Cs_2CO_3 was crucial for a high yield of the desired cycloadduct. What was the role of the added base in the cascade reactions? Was it necessary for the cross-coupling step or for the Diels–Alder reaction step? To make this point clear, the reaction of **1e** with **2a** was performed under neutral conditions at room temperature, and allene **5a** was also produced in 65% yield [Scheme 3, Equation (1)]. The reaction of **1a** with **2a** in the absence of base at 100 °C produced dihy-



Scheme 3. The allenic intermediate and its further transformation.

droanthracen-2-ol **8a**; no oxygen-bridged cycloadduct was obtained [Scheme 3, Equation (3)]. Treatment of **5a** with a Lewis acid resulted in the formation of **8b** and anthracene **4e**; again, no oxygen-bridged cycloadduct was observed [Scheme 3, Equation (4)]. These results suggested that both the cross-coupling and the Diels–Alder reaction could occur without the assistance of base, and the role of the base might be in stabilizing oxygen-bridged compound **3** for a high yield of the isolated product.

On the basis of the above observations and the reported work,[9] a possible reaction mechanism is proposed in Scheme 4. First, oxidative addition of propargyl carbonate **1** to Pd^0 gives allenyl palladium intermediate **6**, which undergoes transmetalation with organoborane **2** to afford **7**. Reductive elimination of **7** produces intermediate **5**. Then, intramolecular Diels–Alder reaction furnishes desired product **3**.



Scheme 4. A proposed reaction pathway.

Conclusions

In conclusion, we showed that oxygen-bridged Diels–Alder cycloadducts could be efficiently prepared by Pd-catalyzed cascade reactions by using propargyl carboxylates bearing a furanyl group with organoborons. Aryl and alkyl substituents on the acetylene terminus were compatible in the intramolecular Diels–Alder reaction of furans reaction, which furnished the desired compounds in good to high yields. The thus-formed oxygen-bridged products were further converted into anthracene derivatives in a chemoselective manner under mild conditions.

Experimental Section

Typical Procedure for the Synthesis of 1,1-Diphenyl-2,10-dihydro-1*H*-2,4a-epoxyanthracene (3a): To a solution of 1-[2-(furan-2-ylmethyl)phenyl]-3-phenylprop-2-yn-1-yl methyl carbonate (**1a**; 69 mg, 0.2 mmol) in THF (2 mL) in a screw-capped tube was added phenylboronic acid (49 mg, 0.4 mmol), $Pd(PPh_3)_4$ (12 mg, 0.01 mmol), and Cs_2CO_3 (130 mg, 0.4 mmol). The resulting solution was stirred at 100 °C for 1 h. Then, the solvent was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 10:1) to afford **3a** (51 mg, 74%) as a yellow solid, m.p. 168–170 °C. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): δ = 3.44 (s, 2 H), 5.53 (d, J = 1.6 Hz, 1 H), 5.92 (dd, J = 1.6, 5.8 Hz, 1 H), 6.41 (s, 1 H), 6.42 (d, J = 5.6 Hz, 1 H), 7.06–7.29 (m, 12 H), 7.43–7.45 (m, 2 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si): δ = 32.92, 59.71, 85.39, 87.92, 122.37, 125.95, 126.39, 126.58, 126.83, 127.14, 127.98, 128.07, 128.14, 128.32, 128.70, 130.58, 133.55, 136.12, 138.84, 144.81, 145.17, 147.22 ppm. HRMS (EI): calcd. for $C_{26}H_{20}O$ 348.1514; found 348.1512.

Typical Procedure for the Synthesis of 1,2-Diphenylanthracene (4c): To a solution of 1,1-diphenyl-2,10-dihydro-1*H*-2,4a-epoxyanthracene (**3a**; 174 mg, 0.5 mmol) in CH_2Cl_2 (5 mL) was added $BF_3{\cdot}OEt_2$ (19 μL, 0.15 mmol). The resulting solution was stirred at room temperature for 1 h. Then, the solvent was evaporated under reduced pressure, and the residue was purified by chromatography on silica gel (petroleum ether/ethyl acetate = 50:1) to afford the product (164 mg, 99%) as a yellow solid, m.p. 139–142 °C. ^{1}H NMR (400 MHz, $CDCl_3$, Me_4Si): δ = 7.16–7.19 (m, 5 H), 7.25–7.39 (m, 7 H), 7.56 (d, J = 9.2 Hz, 1 H), 7.81 (d, J = 8.4 Hz, 1 H), 7.99 (d, J = 8.4 Hz, 1 H), 8.05 (dd, J = 0.4, 8.8 Hz, 1 H), 8.21 (s, 1 H), 8.46 (s, 1 H) ppm. ^{13}C NMR (100.6 MHz, $CDCl_3$, Me_4Si): δ = 125.25, 125.56, 125.85, 126.13, 126.20, 126.82, 127.61, 127.77, 127.87, 127.92, 128.24, 128.64, 130.10, 131.05, 131.34, 131.35, 131.56, 131.86, 137.17, 137.30, 139.10, 142.01 ppm. HRMS (EI): calcd. for $C_{26}H_{18}$ 330.1409; found 330.1413.

Supporting Information (see footnote on the first page of this article): Experimental details, characterization data, and ^{1}H NMR and ^{13}C NMR spectra of all products.

Acknowledgments

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[10] CCDC-952055 (for **3h**), -952056 (for **4a**), -952057 (for **4b**), and -952058 (for **4d**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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