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Pd-catalyzed cyclodimerization of alkenyl and aryl dibromides: Construction of dibenzo[*a,e*]cyclooctatetraenes

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ABSTRACT

Cyclooctatetraenes, including dibenzocyclooctatetraenes, are structurally interesting compounds and are widely used in many areas. Therefore, the development of synthetic methods for such compounds has long been attractive. In this work, a Pd-catalyzed coupling reaction between alkenylbromides and arylbromides has been realized. Multi-substituted 1,4-dibromo-1,3-butadienes and *o*-bromo-2-(2-bromovinyl)benzenes underwent a Pd-catalyzed cyclodimerization reaction to afford the corresponding multi-substituted cyclooctatetraenes and dibenzo[*a,e*]cyclooctatetraenes, respectively, in high yields and with excellent regioselectivity.

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1. Introduction

Multi-substituted cyclooctatetraenes (COTs) and their derivatives such as dibenzocyclooctatetraenes are a class of structurally interesting molecules that are useful organic intermediates [1–6] and sterically demanding ligands for metals [7–10]. Although several general and efficient methods are known for the preparation of multi-substituted COTs [11–17], many of these methods require a stoichiometric amount of lithium [15] or copper reagent [18–25]. Transition metal-catalyzed approaches for multi-substituted COTs mainly focus on the reaction of alkynes [26,27] tricyclo[4.2.0.0^{2,5}]octa-3,7-dienes [28] and biphenylene derivatives [29–33].

Alkenyl dibromides have become important building blocks

in organic synthesis [34–56]. They have been used to synthesize π -conjugated compounds via their corresponding lithium reagents [41–44], and pyrrole derivatives via a transition metal-catalyzed direct amination reaction [45–50]. We and others have developed efficient synthetic methods for dibromides *o*-bromo-2-(2-bromovinyl)benzenes (**1**) and 1,4-dibromo-1,3-butadienes (**2**) (Scheme 1) [35,50–52]. Compounds such as these can be used in the synthesis of novel organometallic and organic compounds by taking advantage of their co-operative effect [22,53–56].

In principle, cyclic dimerization of functionalized dibromides **1** or **2** would afford cyclooctatetraenes and their derivatives. Such a strategy has been applied by Takahashi et al. [18], Itoh et al. [23,24], Xi et al. [25] and our group [19–22,57] when

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Scheme 1. Synthesis of cyclooctatetraenes and their derivatives from alkenyl and aryl dibromides.

one or two of the halogen atoms are replaced by Cu or Bpin (Scheme 1). In this work, we would like to report the first catalytic and direct homo-coupling of dibromides **1** or **2** for the synthesis of dibenzo[a,e]cyclooctatetraenes and cyclooctatetraenes (Scheme 1).

2. Experimental

2.1. General

Unless otherwise noted, all starting materials were commercially available and were used without further purification. All reactions were carried out using standard Schlenk techniques or under a nitrogen atmosphere in a glovebox. The nitrogen in the glovebox was constantly circulated through a copper/molecular sieve catalyst unit. The oxygen and moisture concentrations in the glovebox atmosphere were monitored by an O₂/H₂O Combi-Analyzer to ensure both were always below 1 ppm. Solvents were purified by an Mbraun SPS-800 Solvent Purification System and dried over fresh Na chips in the glovebox. ¹H and ¹³C NMR spectra were recorded on a Bruker ARX 400 spectrometer (FT, 400 MHz for ¹H; 100 MHz for ¹³C) or a Bruker AVANCE III 500 spectrometer (FT, 500 MHz for ¹H; 125 MHz for ¹³C) at room temperature in a CDCl₃ solution with tetramethylsilane (0.00 ppm) as the internal standard, unless otherwise noted. High-resolution mass spectra (HRMS) were recorded on a Bruker Apex IV FTMS mass spectrometer using ESI and FT-ICR mass analyzer or a Bruker Daltonics Inc APEXII mass spectrometer using EI and FT-ICR mass analyzer. GC/MS

analyses were recorded on Agilent 7890A/5975C using EI MSD.

2.2. Preparation of dibenzocyclooctatetraenes and octaethylcyclooctatetraene

The dibromo-substituted vinyl compounds **1** and **2** were prepared according to literature methods [50–52]. A dibromo-substituted substrate (0.6 mmol, 2 eq.), Pd(*t*-Bu₃P)₂ (0.015 mmol, 5 mol%), *t*-Bu₃P (0.03 mmol, 10 mol%), and LiOEt (1.2 mmol, 4 eq.) were added to 5 mL toluene. The mixture was stirred at 120 °C for 24 h. The reaction mixture was quenched with water and extracted with ethyl acetate. The organic extract was washed with brine and dried over Na₂SO₄. The solvent was then evaporated in vacuo and the residue was purified using a silica gel column, eluting with petroleum ether and ethyl acetate, to afford the multi-substituted cyclooctatetraenes **3** and **4**.

2.3. Analytical data for the dibromides **1**

(*Z*)-1-Bromo-2-(3-bromobut-2-en-2-yl)benzene (**1c**). White solid, isolated yield 95% (547 mg); m.p.: 33.8–34.7 °C; ¹H NMR (400 MHz, CDCl₃) δ: 1.93 (s, 3H), 2.37 (s, 3H), 7.02–7.06 (m, 2H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.51 (d, *J* = 8.1 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ: 20.16 (1 CH₃), 24.77 (1 CH₃), 118.68 (1 quat. C), 121.61 (1 quat. C), 127.27 (1 CH), 128.26 (1 CH), 129.30 (1 CH), 132.36 (1 CH), 135.05 (1 quat. C), 145.04 (1 quat. C); HRMS (ESI, *m/z*) calcd. for C₁₀H₁₁Br₂ [M+H]⁺: 288.9222; Found 288.9219.

(*Z*)-1-Bromo-2-(1-bromo-1-phenylbut-1-en-2-yl)benzene (**1d**). White solid, isolated yield 85% (619 mg); m.p.: 34.9–38.31 °C; ¹H NMR (400 MHz, CDCl₃) δ: 0.91 (t, *J* = 7.5 Hz, 3H), 2.29–2.44 (m, 2H), 7.12–7.34 (m, 5H), 7.36–7.42 (m, 2H), 7.45–7.47 (m, 1H), 7.65 (d, *J* = 7.6 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ: 12.60 (1 CH₃), 28.38 (1 CH₂), 120.90 (1 quat. C), 122.64 (1 quat. C), 127.18 (1 CH), 128.35 (3 CH), 128.72 (1 CH), 128.84 (2 CH), 130.27 (1 CH), 132.82 (1 CH), 140.13 (1 quat. C), 142.65 (1 quat. C), 143.53 (1 quat. C); HRMS (ESI, *m/z*) calcd. for C₁₆H₁₅Br₂ [M+H]⁺: 364.9535; Found 364.9545.

(*Z*)-1-Bromo-2-(5-bromo-4-en-4-yl)-4-fluorobenzene (**1e**). Yellow oil, isolated yield 91% (662 mg); ¹H NMR (400 MHz, CDCl₃) δ: 0.90 (t, *J* = 7.2 Hz, 3H), 1.01 (t, *J* = 7.4 Hz, 3H), 1.23–1.43 (m, 2H), 1.64–1.77 (m, 2H), 2.23–2.49 (m, 2H), 2.51–2.74 (m, 2H), 6.80 (dd, *J* = 8.9, 3.0 Hz, 1H), 7.01 (dd, *J* = 7.7, 2.2 Hz, 1H), 7.51 (d, *J* = 8.8 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ: 13.18 (1 CH₃), 13.96 (1 CH₃), 21.03 (1 CH₂), 21.65 (1 CH₂), 36.00 (1 CH₂), 38.66 (1 CH₂), 114.28 (d, *J* = 21.0 Hz, 1 CH), 119.84 (d, *J* = 24.3 Hz, 1 CH), 122.60 (d, *J* = 9.5 Hz, 1 quat. C), 127.48 (1 quat. C), 131.31 (d, *J* = 8.3 Hz, 1 CH), 139.18 (d, *J* = 1.2 Hz, 1 quat. C), 145.73 (d, *J* = 8.0 Hz, 1 quat. C), 161.16 (d, *J* = 248.5 Hz, 1 quat. C); HRMS (EI, *m/z*) calcd. for C₁₄H₁₇Br₂F [M]⁺: 363.9661; Found 363.9659.

(*Z*)-1-Bromo-2-(5-bromo-4-en-4-yl)-4-methylbenzene (**1f**). Colorless oil, isolated yield 91% (652 mg); ¹H NMR (400 MHz, CDCl₃) δ: 0.89 (t, *J* = 7.2 Hz, 3H), 1.02 (t, *J* = 7.2 Hz, 3H), 1.26–1.44 (m, 2H), 1.65–1.76 (m, 2H), 2.24–2.31 (m, 4H, CH₃+CH₂), 2.42–2.50 (m, 1H), 2.53–2.73 (m, 2H), 6.93 (d, *J* = 7.8

Hz, 1H), 7.08 (d, J = 8.6 Hz, 1H), 7.41 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 13.19 (1 CH_3), 13.99 (1 CH_3), 20.77 (1 CH_3), 21.05 (1 CH_2), 21.68 (1 CH_2), 36.11 (1 CH_2), 38.68 (1 CH_2), 122.17 (1 quat. C), 126.74 (1 quat. C), 127.83 (1 CH), 130.12 (1 CH), 133.07 (1 CH), 138.38 (1 quat. C), 139.89 (1 quat. C), 141.12 (1 quat. C); HRMS (ESI, m/z) calcd. for $\text{C}_{15}\text{H}_{21}\text{Br}_2$ $[\text{M}+\text{H}]^+$: 359.0005; Found 359.0009.

(Z)-1-Bromo-2-(5-bromooct-4-en-4-yl)-4-methoxybenzene (**1g**). Colorless oil, isolated yield 93% (710 mg); ^1H NMR (400 MHz, CDCl_3) δ : 0.90 (t, J = 7.3 Hz, 3H), 1.01 (t, J = 7.4 Hz, 3H), 1.26–1.48 (m, 2H), 1.67–1.76 (m, 2H), 2.24–2.48 (m, 2H), 2.51–2.73 (m, 2H), 3.79 (s, 3H), 6.84 (d, J = 8.5, 1H), 6.96 (d, J = 8.5 Hz, 1H), 7.13 (s, 1H); ^{13}C NMR (100 MHz, CDCl_3) δ : 13.19 (1 CH_3), 13.99 (1 CH_3), 21.05 (1 CH_2), 21.69 (1 CH_2), 36.22 (1 CH_2), 38.73 (1 CH_2), 55.39 (1 CH_3), 113.24 (1 CH), 117.61 (1 CH), 122.71 (1 quat. C), 127.23 (1 quat. C), 130.85 (1 CH), 136.50 (1 quat. C), 139.66 (1 quat. C), 158.81 (1 quat. C); HRMS (ESI, m/z) calcd. for $\text{C}_{15}\text{H}_{21}\text{Br}_2\text{O}$ $[\text{M}+\text{H}]^+$: 374.9954; Found 374.9965.

2.4. Analytical data for the COT derivatives

(5Z,11Z)-5,6,11,12-Tetrapropylidibenzo[*a,e*]cyclooctatetraene (**3a**) [19]. Yellow oil, isolated yield 83% (93 mg); ^1H NMR (400 MHz, CDCl_3) δ : 0.95 (t, J = 7.6 Hz, 12H), 1.42–1.51 (m, 8H), 2.35–2.43 (m, 8H), 6.91–6.97 (m, 8H); ^{13}C NMR (100 MHz, CDCl_3) δ : 14.66 (4 CH_3), 22.43 (4 CH_2), 36.68 (4 CH_2), 125.40 (4 CH), 126.63 (4 CH), 137.97 (4 quat. C), 143.23 (4 quat. C).

(5Z,11Z)-5,6,11,12-Tetraethylidibenzo[*a,e*]cyclooctatetraene (**3b**) [19]. Yellow oil, isolated yield 74% (70 mg); ^1H NMR (400 MHz, CDCl_3) δ : 1.06 (t, J = 7.6 Hz, 12H), 2.41–2.54 (m, 8H), 6.94–6.99 (m, 8H); ^{13}C NMR (100 MHz, CDCl_3) δ : 14.03 (4 CH_3), 27.15 (4 CH_2), 125.46 (4 CH), 126.65 (4 CH), 138.72 (4 quat. C), 143.04 (4 quat. C).

(5Z,11Z)-5,6,11,12-Tetramethylidibenzo[*a,e*]cyclooctatetraene (**3c**). White solid, isolated yield 85% (66 mg); m.p.: 155.4–157.1 °C; ^1H NMR (400 MHz, CDCl_3) δ : 2.05 (s, 12H), 6.95–7.01 (m, 8H); ^{13}C NMR (100 MHz, CDCl_3) δ : 21.03 (4 CH_3), 125.77 (4 CH), 126.76 (4 CH), 132.51 (4 quat. C), 143.52 (4 quat. C); HRMS (ESI, m/z) calcd. for $\text{C}_{20}\text{H}_{24}$ $[\text{M}+\text{H}]^+$: 261.1638; Found 261.1641.

(5Z,11Z)-5,11-Diethyl-6,12-diphenylidibenzo[*a,e*]cyclooctatetraene (**3d**). Yellow oil, isolated yield 66% (81 mg); ^1H NMR (400 MHz, CDCl_3) δ : 0.41 (t, J = 7.5 Hz, 6H), 2.16–2.25 (m, 4H), 6.78–6.80 (m, 4H), 7.10–7.13 (m, 4H), 7.28–7.44 (m, 10H); ^{13}C NMR (125 MHz, CDCl_3) δ : 12.53 (2 CH_3), 27.91 (2 CH_2), 126.21 (2 CH), 126.24 (2 CH), 126.65 (2 CH), 126.80 (2 CH), 127.55 (4 CH), 128.66 (2 CH), 129.18 (4 CH), 139.41 (2 quat. C), 140.20 (4 quat. C), 142.53 (2 quat. C), 142.63 (2 quat. C); HRMS (ESI, m/z) calcd. for $\text{C}_{32}\text{H}_{29}$ $[\text{M}+\text{H}]^+$: 413.2264; Found 413.2271.

(5Z,11Z)-2,8-Difluoro-5,6,11,12-tetrapropylidibenzo[*a,e*]cyclooctatetraene (**3e**). Colorless oil, isolated yield 66% (81 mg); ^1H NMR (400 MHz, CDCl_3) δ : 0.93–0.98 (m, 12H), 1.39–1.48 (m, 8H), 2.33–2.37 (m, 8H), 6.61–6.71 (m, 4H), 6.86–6.90 (m, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : 14.59 (4 CH_3), 22.31 (2 CH_2), 22.40 (2 CH_2), 36.67 (4 CH_2), 112.72 (d, J = 21.1 Hz, 2 CH), 113.07 (d, J = 20.4 Hz, 2 CH), 128.17 (d, J = 8.2 Hz, 2 CH), 137.63 (d, J = 1.5 Hz, 2 quat. C), 137.91 (2 quat. C), 138.76 (d, J = 3.0 Hz, 2 quat. C), 145.06 (d, J = 7.2 Hz, 2 quat. C), 160.73 (d, J = 242.8

Hz, 2 quat. C); HRMS (ESI, m/z) calcd. for $\text{C}_{28}\text{H}_{35}\text{F}_2$ $[\text{M}+\text{H}]^+$: 409.2701; Found 409.2707.

(5Z,11Z)-2,8-Dimethyl-5,6,11,12-tetrapropylidibenzo[*a,e*]cyclooctatetraene (**3f**). Yellow oil, isolated yield 70% (84 mg); ^1H NMR (400 MHz, CDCl_3) δ : 0.92–0.97 (m, 12 H), 1.40–1.49 (m, 8H), 2.17 (s, 6H), 2.32–2.36 (m, 8H), 6.75–6.84 (m, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ : 14.68 (4 CH_3), 21.12 (2 CH_3), 22.52 (4 CH_2), 36.86 (4 CH_2), 126.27 (2 CH), 126.44 (2 CH), 127.26 (2 CH), 134.48 (2 quat. C), 137.71 (2 quat. C), 137.87 (2 quat. C), 140.46 (2 quat. C), 143.21 (2 quat. C); HRMS (ESI, m/z) calcd. for $\text{C}_{30}\text{H}_{41}$ $[\text{M}+\text{H}]^+$: 401.3203; Found 401.3205.

(5Z,11Z)-2,8-Dimethoxy-5,6,11,12-tetrapropylidibenzo[*a,e*]cyclooctatetraene (**3g**). Yellow oil, isolated yield 73% (95 mg); ^1H NMR (400 MHz, CDCl_3) δ : 0.92–0.96 (m, 12 H), 1.41–1.49 (m, 8H), 2.31–2.38 (m, 8H), 3.69 (s, 6H), 6.48 (s, 2H), 6.55 (d, J = 8.5 Hz, 2H), 6.85 (d, J = 8.5 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ : 14.65 (4 CH_3), 22.47 (2 CH_2), 22.57 (2 CH_2), 36.88 (4 CH_2), 54.93 (2 CH_3), 111.07 (2 CH), 111.99 (2 CH), 127.50 (2 CH), 136.01 (2 quat. C), 137.67 (2 quat. C), 137.85 (2 quat. C), 144.50 (2 quat. C), 156.98 (2 quat. C); HRMS (ESI, m/z) calcd. for $\text{C}_{30}\text{H}_{41}\text{O}_2$ $[\text{M}+\text{H}]^+$: 433.3101; Found 433.3092.

Tetraphenylene (**3h**). White solid, isolated yield 74% (41 mg) [58]; ^1H NMR (400 MHz, CDCl_3) δ : 7.13–7.17 (m, 8 H), 7.25–7.28 (m, 8H); ^{13}C NMR (125 MHz, CDCl_3) δ : 127.22 (8 CH), 129.01 (8 CH), 141.55 (8 quat. C).

(1Z,3Z,5Z,7Z)-1,2,3,4,5,6,7,8-Octaethylcycloocta-1,3,5,7-tetraene (**3i**) [20]. Colorless oil, isolated yield 61% (60 mg); ^1H NMR (400 MHz, CDCl_3) δ : 0.94 (t, J = 7.5, 24H), 1.97–2.11 (m, 16H); ^{13}C NMR (100 MHz, CDCl_3) δ : 14.22 (8 CH_3), 23.54 (8 CH_2), 138.32 (8 quat. C).

2.5. X-ray crystallographic studies of **3c**

Single crystals of **3c** suitable for X-ray analysis were grown in solution of CDCl_3 . Data collection for **3c** was performed at –93 °C on a Rigaku CCD SATURN724 diffractometer using graphite-monochromated $\text{Mo K}\alpha$ radiation (λ = 0.71073 Å). The structures were solved using the SHELXTL program [59] or with the XS [60] structure solution program using Direct Methods and refined with the olex2.refine refinement package using Gauss-Newton minimization [60,61]. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. CCDC 1006078 (**3c**).

3. Results and discussion

3.1. Optimization of reaction conditions

Initially, we investigated the reaction of **1a**, which afforded the dibenzo[*a,e*]cyclooctatetraene derivative **3a**. Various reaction conditions were screened (Table 1). We found that the reaction was very sensitive to the choice of base [62]. LiOEt was found to be the most effective base for this reaction, while stronger bases (e.g. NaOt-Bu and KOt-Bu) resulted in the decomposition of **1a** and weak bases (e.g. NaOAc) afforded no product at all (entries 3–5). The amount of the base used in this

Table 1
Optimization of reaction conditions.

Entry	[Pd]	Ligand	Base	Yield of 3a ^a (%)
1	PdCl ₂ (PhCN) ₂	<i>t</i> -Bu ₃ P	LiOt-Bu	trace
2	PdCl ₂ (PPh ₃) ₂	<i>t</i> -Bu ₃ P	LiOt-Bu	trace
3	PdCl ₂ (PPh ₃) ₂	<i>t</i> -Bu ₃ P	NaOt-Bu	trace
4	PdCl ₂ (PPh ₃) ₂	<i>t</i> -Bu ₃ P	KOt-Bu	— ^b
5	PdCl ₂ (PPh ₃) ₂	<i>t</i> -Bu ₃ P	NaOAc	— ^b
6	PdCl ₂ (PPh ₃) ₂	<i>t</i> -Bu ₃ P	Cs ₂ CO ₃ ^c	10
7	PdCl ₂ (PPh ₃) ₂	<i>t</i> -Bu ₃ P	LiOEt	85
8	PdCl ₂ (PPh ₃) ₂	P(2-furan) ₃	LiOEt	67
9	PdCl ₂ (PPh ₃) ₂	Sphos	LiOEt	53
10	PdCl ₂ (PPh ₃) ₂	PPh ₃	LiOEt	42
11	Pd(<i>t</i> -Bu ₃ P) ₂	<i>t</i> -Bu ₃ P	LiOEt	89(83)
12	Pd(<i>t</i> -Bu ₃ P) ₂	—	LiOEt	41
13	Pd(<i>t</i> -Bu ₃ P) ₂	—	LiOt-Bu	trace
14	Pd(<i>t</i> -Bu ₃ P) ₂	—	LiOt-Bu ^c	47
15	Pd(<i>t</i> -Bu ₃ P) ₂	<i>t</i> -Bu ₃ P	LiOEt ^d	trace
16	Pd(<i>t</i> -Bu ₃ P) ₂	<i>t</i> -Bu ₃ P	LiOEt ^e	11
17	Pd(<i>t</i> -Bu ₃ P) ₂	<i>t</i> -Bu ₃ P	LiOEt ^f	35
18	Pd(<i>t</i> -Bu ₃ P) ₂	<i>t</i> -Bu ₃ P	LiOEt ^g	70

^a GC yield (*n*-C₁₂H₂₆ as internal standard), isolated yield in parenthesis.

^b No product was observed.

^c 4 eq. of *i*-PrOH was added.

^d 0.5 eq. of LiOEt was used.

^e 1.0 eq. of LiOEt was used.

^f 2.0 eq. of LiOEt was used.

^g 3.0 eq. of LiOEt was used.

reaction strongly affected the yield of product **3a** (entries 11, 15–18). The optimum conditions for this transformation were found to be Pd(*t*-Bu₃P)₂ (5 mol%), *t*-Bu₃P (10 mol%), LiOEt (4 equiv), toluene, 120 °C, 24 h. Under these optimized reaction conditions, the product **3a** was obtained in 83% isolated yield.

3.2. Reaction scope

With the above optimized reaction conditions in hand, we investigated the scope of this reaction. As shown in Scheme 2, dibenzo[*a,e*]cyclooctatetraene derivatives **3a–3h** could be obtained in moderate to good yields. The substituents in the vinyl group played an important role in this reaction. Those substrates substituted with aliphatic groups reacted smoothly and **3a–3c** were generated in good yields. Changing the aliphatic group to an aromatic one caused a slight decrease in the yield (**3d**). A phenyl ring substituted with different groups generally afforded moderate to good yields of the corresponding products (**3e–3g**). Those substituted with electron-donating groups gave the products in slightly higher yields than those with the electron-withdrawing ones. The tetraphenylene product **3h** could also be obtained in this reaction. It is noteworthy that this coupling reaction proceeded highly selectively. The stereochemistry of compound **3c** was determined by its single crystal X-ray structural analysis (Fig. 1).

Scheme 2. Formation of dibenzo[*a,e*]cyclooctatetraenes **3** via intramolecular homo-coupling of *o*-bromo-(2-bromovinyl)benzenes **1**.

Fig. 1. ORTEP drawing of **3c** with 30% thermal ellipsoids. Hydrogen atoms omitted for clarity.

Meanwhile, the 1,2,3,4-tetraethyl-1,4-dibromo-1,3-butadiene **2** could also be reacted to afford the corresponding octaethylcyclooctatetraene **3i** (Scheme 3).

3.3. Reaction mechanism

To gain insight into this reaction, several experiments were carried out. (1) As shown in Table 1, only a trace amount of **3a**

Scheme 3. Formation of octaethylcyclooctatetraene **3i** via intramolecular homo-coupling of 1,2,3,4-tetraethyl-1,4-dibromo-1,3-butadiene **2**.

could be observed in the presence of 0.5 eq. LiOEt and mainly starting material **1a** remained. Increasing the amount of LiOEt enhanced the yield of **1a** (Table 1, entries 11 and 15–18). (2) Lemaire et al. [63,64] reported that *i*-PrOH could be used as a reducing agent to regenerate the Pd(0) active species from Pd(II) species with the concomitant formation of acetone. In this COT formation reaction, both the gas and the liquid phases of the reaction were analyzed using GC/MS analysis. The examination of the reaction mixture showed that small amounts of acetaldehyde and ethyl acetate were formed in this process [65]. (3) The addition of a reductant (e.g. *i*-PrOH) was essential when LiOt-Bu was used instead of LiOEt in this reaction (Table 1, entries 13 and 14).

Based on the above preliminary results, a plausible catalytic cycle for the formation of cyclooctatetraene is shown in Scheme 4 [57,66–70]. Intermediate **5** would be generated via oxidative addition of **1** to the Pd(0) species. Then ligand exchange and a

subsequent intramolecular migratory insertion would lead to the formation of palladacycle intermediate **6**. This palladacycle could undergo a second oxidative addition with another molecule of **1** to generate intermediate **7** and a subsequent reductive elimination would give intermediate **8**. A second ligand exchange followed by intramolecular migratory insertion would lead to the formation of the 9-membered palladacycle intermediate **9**. Finally, reductive elimination of **9** would then release the cyclooctatetraene **3** and regenerate the active Pd(0) species to re-enter the catalytic cycle.

As reported in our previous work [57], dibenzo[*a,c*]cyclooctatetraenes could be selectively generated via a Pd-catalyzed homo-coupling of borylvinyl iodobenzene derivatives (Scheme 5, Eq. 1). A control experiment was carried out to investigate the different selectivity of these two reactions. When **1a** was treated with PdCl₂(PPh₃)₂, *i*-PrOH and Cs₂CO₃, formation of trace amounts of both **3a** and **3a'** could be observed, along with the remaining starting material **1a** (Scheme 5, Eq. 2). The addition of 10 mmol% of *t*-Bu₃P led to trace amounts of **3a'** and 10% of **3a** with remaining **1a** (Table 1, entry 6). The different selectivity could be explained by the steric effects of the ligand. When Cs₂CO₃ is added to the reaction, it can act as a carboxylate ligand, coordinating to the Pd(IV) center. The corresponding Pd(IV) intermediate **7'** would therefore have a different configuration to intermediate **7**, and thus result in different selectivity in the subsequent reductive elimination (Scheme 5).

Scheme 4. A proposed mechanism of the formation of cyclooctatetraenes.

Scheme 5. Steric effects of ligands in the regioselective generation of cyclooctatetraenes.

4. Conclusions

We have developed an efficient Pd-catalyzed intramolecular homo-coupling reaction of dibromo-substituted compounds to synthesize multi-substituted cyclooctatetraenes, in particular dibenzo[*a,e*]cyclooctatetraene derivatives. We propose that the steric effects of the ligands control the regioselectivity of the formation of the dibenzocyclooctatetraenes.

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Graphical Abstract

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Pd-catalyzed cyclodimerization of alkenyl and aryl dibromides: Construction of dibenzo[*a,e*]cyclooctatetraenes

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Dibenzo[*a,e*]cyclooctatetraene derivatives are efficiently and regioselectively generated from a palladium-catalyzed [4+4] cyclic homo-coupling of *o*-bromo-2-(2-bromovinyl)benzenes.

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钯催化二溴代化合物自偶联环化合成二苯并[*a,e*]环辛四烯

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摘要: 由于独特的结构和广泛的应用, 多取代环辛四烯及其苯并稠环衍生物的合成方法研究具有重要意义. 本文报道了一种钯催化烯基溴化物与芳基溴化物的偶联反应. 利用此钯催化的环化自偶联反应, 以中等至较好的收率高选择性地从双溴代芳基或烯基化合物合成了多种二苯并[*a,e*]环辛四烯衍生物.

关键词: 二溴代化合物; 环辛四烯; 二苯并[*a,e*]环辛四烯; 1,3-丁二烯; 自偶联反应; 钯催化剂

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1. 前言

多取代环辛四烯及其衍生物(如二苯并环辛四烯)因其独特的结构带来的特殊性质和反应性而成为一种重要的有机合成中间体^[1-6]和金属配体^[7-10]. 目前已有一些方法可以较高效地合成多取代环辛四烯^[11-17], 但这些方

法大部分都需要使用当量的有机锂试剂^[15]或有机铜试剂^[18-25]. 过渡金属催化的环辛四烯的合成多集中在炔烃^[26,27]、三环[4.2.0.0^{2,5}]辛-3,7-二烯^[28]和联苯撑类化合物^[29-35]的反应上.

烯基溴化物是一类重要的有机合成子^[34-56]. 其可通过锂卤交换反应制备相应的有机锂试剂进而合成大 π 共

轭体系^[41–44],或通过过渡金属催化的胺化反应直接合成吡咯衍生物^[45–50].本课题组和其他课题组发展了一系列能高效合成1,4-二溴-1,3-丁二烯类化合物的方法^[35,50–52],并利用此类二溴化合物骨架的协同效应将其应用到新型金属有机化合物和有机小分子化合物的合成中^[22,53–56].

从原理上看,利用官能团化(如金属化)的1,3-丁二烯衍生物的自偶联反应来制备多取代环辛四烯是一个可行的方法.这种策略已经被Takahashi等^[18]、Itoh等^[23,24]、Xi等^[25]和本课题组^[19–22,57]所采用(图式1).本文发展了一种利用钯催化二溴代化合物的[4+4]自偶联反应来合成多取代环辛四烯和二苯并[*a,e*]环辛四烯的方法(图式1).

2. 实验部分

2.1. 试剂和仪器

如无特别说明,所有原料均从试剂公司购得后未作任何纯化处理直接使用,所有反应均采用标准Schlenk技术在高纯氮气正压下或在Mikrouna Super (1220/750)手套箱中进行.手套箱中的氮气在铜/分子筛催化剂单元中不断循环通过,并使用水氧联合分析仪进行监测,以保证水氧含量始终处于1 ppm以下.溶剂四氢呋喃(THF)和甲苯由Mbraun SPS-800溶剂处理系统除水除氧后加入钠丝存放于手套箱保存.柱层析所用石油醚沸程为60–90 °C.¹H NMR和¹³C NMR核磁共振谱由Bruker ARX400核磁共振谱仪(¹H谱400 MHz, ¹³C谱100 MHz)和Bruker ARX500核磁共振谱仪(¹H谱500 MHz, ¹³C谱125 MHz)在室温下测得,所用溶剂为氘代氯仿(CDCl₃),除特别说明外以四甲基硅烷(0.00 ppm)作为内标.傅里叶变换高分辨质谱(HMRS)测试分别采用Bruker Apex IV电喷雾电离(ESI)和傅里叶变换离子回旋共振(FT-ICR)质谱仪,以及Bruker Daltonics Inc APEXII电子轰击(EI)和傅里叶变换离子回旋共振(FT-ICR)质谱仪.气相色谱质谱联用仪(GC/MS)检测采用电子轰击(EI)检测器.

2.2. 二苯并环辛四烯和多取代环辛四烯的合成

二溴化合物**1**和**2**采用文献报道的方法合成^[50–52].在氮气保护下,向25 mL的Schlenk管中依次加入二溴化合物(0.6 mmol, 2 equiv.), Pd(*t*-Bu₃P)₂ (0.015 mmol, 5 mol%), *t*-Bu₃P (0.03 mmol, 10 mol%), LiOEt (1.2 mmol, 4 equiv.)和5 mL甲苯.将反应管置于120 °C油浴中搅拌反应24 h后将反应管冷却至室温.反应混合物用水淬灭后使用乙酸乙酯萃取,得到的有机溶液在使用饱和NaCl溶液洗涤和无水Na₂SO₄干燥后减压蒸馏除去溶剂.所得粗产物使用

硅胶柱色谱进行分离,即可得到多取代环辛四烯产物**3**和**4**,洗脱液为石油醚和乙酸乙酯混合溶剂.

2.3. 二溴化合物**1**的表征数据

(略,见英文部分)

2.4. 多取代环辛四烯**3**和**4**的表征数据

(略,见英文部分).

2.5. **3c**的单晶结构表征

将**3c**的氘代氯仿溶液在室温下挥发1 d,可得到适合X射线单晶衍射结构测试的晶体.该晶体用Rigaku CCD SATURN724型X射线衍射仪在–98 °C采用经石墨单色化的Mo K_α射线(λ=0.71073 Å)收集衍射数据.结构用直接法(SHELXTL-97)解出^[59,60],晶体结构修正用olex2程序^[60,61],氢原子坐标由差值Fourier合成法得到.以上单晶数据可通过剑桥晶体数据库(www.ccdc.cam.ac.uk/data_request/cif)进行检索.CCDC 1006078 (**3c**).

3. 结果与讨论

3.1. 反应条件优化

如表1所示,本文首先选择**1a**的反应作为模型反应进行考察.反应在特定条件下可以得到目标产物二苯并[*a,e*]环辛四烯**3a**.值得注意的是,除了不同的催化剂和配体在反应中所表现出来的差别外,碱的选择对该转化过程十分敏感^[62].经筛选发现, LiOEt是最有效的碱,使用较强的碱(如NaO*t*-Bu和KO*t*-Bu)会导致**1a**分解,而使用较弱的碱(如NaOAc)则不能得到相应产物(表1,实验3–5).反应中碱的用量也会显著影响**3a**的产率(表1,实验11和15–18).表1中还列出了其他一些反应条件的筛选结果.最终确定的最佳反应条件为: Pd(*t*-Bu₃P)₂ (5 mol%), *t*-Bu₃P (10 mol%), LiOEt (4 equiv.)在甲苯中120 °C反应24 h.此时相应产物**3a**的分离收率可达83%.

3.2. 底物拓展

在最优反应条件下,本文以中等至较好的收率合成了一系列环辛四烯衍生物**3a–3h**(图式2).底物中烯基上的取代基对反应产率有很大影响.当底物双键上为两个烷基时,可以高产率获得相应产物**3a–3c**.将底物双键上的一个烷基换为苯基时,相应产物的产率会有明显降低(**3d**).底物中苯环上有不同取代基时也能顺利反应得到相应的产物(**3e–3g**).含有供电子基团的底物的反应产率比含有吸电子基团的底物高.四邻亚苯**3h**也可以通过此反应制备.值得注意的是,此反应有很高的选择性.产物**3c**的结构已经通过X射线单晶衍射确认(图1).

与此同时,1,2,3,4-四乙基-1,4-二溴-1,3-丁二烯(**2**)也

可以在此条件下顺利反应,得到相应的环辛四烯产物**3i**(图式3).

3.3. 机理研究

为了阐明该自偶联反应的机理,本文进行了一系列的验证实验. (1) 在仅加入0.5当量LiOEt进行反应时,只能观察到痕量的**3a**生成,同时伴随原料剩余;增加LiOEt用量可有效提高**3a**产率(表1,实验11和15–18). (2) 文献曾报道^[63,64]异丙醇可用作还原剂原位将反应体系中的Pd(II)物种还原为活性的Pd(0)物种,同时自身被氧化为丙酮. 本文作者使用气相色谱质谱联用仪对本自偶联反应的气相和液相部分分别进行了原位检测,发现在此反应中有乙醛和乙酸乙酯生成^[65]. (3) 将反应中使用的碱更换为LiO*t*-Bu后,则必须加入还原剂(如异丙醇)该反应才能顺利进行(表1,实验13和14).

基于以上实验,本文提出了以下可能的反应机理^[57,66–70](图式4). 首先, Pd(0)物种对底物**1**进行氧化加成,得到中间体**5**. 中间体**5**上的配体与LiOEt中的乙氧基进行配体交换反应后,发生分子内迁移插入反应,得到钯杂环中间体**6**. 此钯杂环与底物再次发生氧化加成反应,得到中间体**7**. 中间体**7**发生还原消除生成中间体**8**,接着发生第二次配体交换反应和分子内迁移插入反应,得到

钯杂九元环中间体**9**. 最后, 中间体**9**发生还原消除反应得到最终的环辛四烯产物**3**,同时再生出活性Pd(0)物种.

本课题组曾经报道过一例钯催化含有烯基硼官能团的碘苯衍生物的自偶联环化生成二苯并[*a,c*]环辛四烯的反应^[57](图式5, 反应式1). 为了研究这两个自偶联反应的不同选择性,作者进行了如下的对比实验. 当向反应管中依次加入底物**1a**, PdCl₂(PPh₃)₂, *i*-PrOH, Cs₂CO₃和甲苯进行反应,能够同时观察到痕量的**3a**和**3a'**两种产物的生成,同时原料**1a**剩余(图式5, 反应式2). 向此反应体系中添加10 mmol%的*t*-Bu₃P进行反应,则能观察到痕量的**3a'**和10%的**3a**生成,同时其余原料**1a**剩余(表1, 实验6). 这表明,这两个反应中不同的选择性可能是配体的立体效应造成的. 当反应中的碱选用Cs₂CO₃时, CO₃²⁻可以作为配体与Pd(IV)金属中心配位,使得相应的中间体**7'**与中间体**7**的构型不相同,进而导致了其后的还原消除中的不同选择性(图式5).

4. 结论

本文发展了一种利用钯催化二溴代化合物的[4+4]自偶联反应合成环辛四烯衍生物的方法. 在此反应中,配体的空间效应可能是影响反应区域选择性的原因.