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Construction of Octaalkyl-Substituted and Decasubstituted *all-cis*-Octatetraenes via Linear Dimerization of 1,4-Dicopper-1,3-butadienes and Subsequent Cross-Coupling with Halides

Junnian Wei,† Zitao Wang,† Wen-Xiong Zhang,† and Zhenfeng Xi*,†,‡

Beijing National Laboratory of Molecular Sciences (BNLMS) and Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871, China, and State Key Laboratory of Organometallic Chemistry, Shanghai Institute of Organic Chemistry, CAS, Shanghai 200032, China

zfxi@pku.edu.cn

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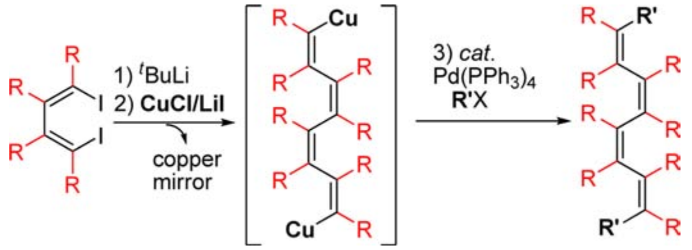
ABSTRACT



Lithium iodide-assisted linear dimerization of 1,4-dicopper-1,3-butadienes and subsequent Pd-catalyzed cross-coupling reaction with halides provide an efficient way to construct octaalkyl-substituted and decasubstituted *all-cis* octatetraenes.

Conjugated polyenes have received intense interest in recent decades because of their unique electronic structures and optoelectronic properties.[1,2] The introduction of alkyl substituents onto the conjugated backbone is a good way to solve the insolubility, infusibility, and instability problems of such compounds. Therefore, it is of significant value to develop methods for alkyl-substituted short polyenes as models.[3] Stereocontrolled short polyenes are usually synthesized by cross-coupling reactions via multistep procedures.[4] Recently, Takahashi et al. reported a regioselective synthesis of substituted *trans*-tetraenes[5a,b] by oligomerization of alkynes. Wu et al. reported a nickel-catalyzed

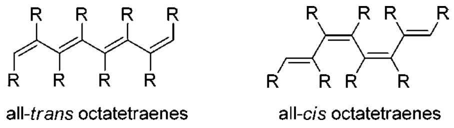


Figure 1. Stereocontrolled all-substituted octatetraenes.

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† Peking University.

‡ Shanghai Institute of Organic Chemistry, CAS.

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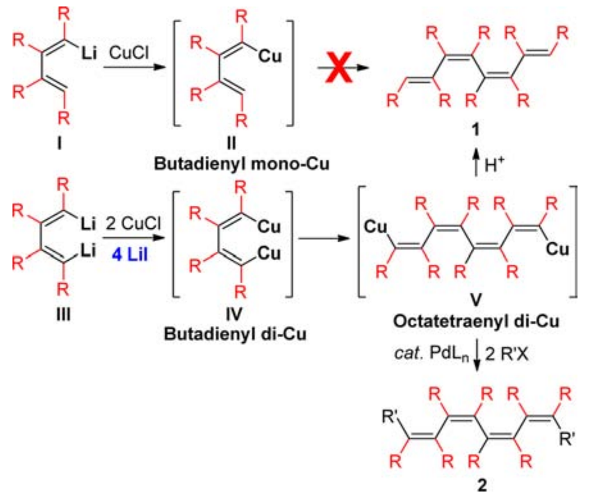
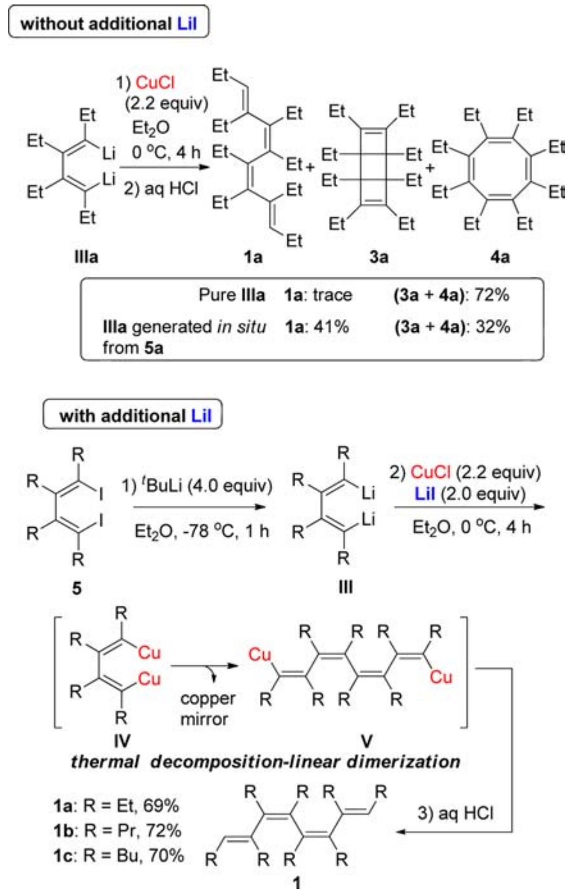
Scheme 1. Thermal Decomposition−Linear Dimerization of Butadienyl Dicopper Compounds



Scheme 2. CuCl/LiI-Mediated Dimerization of 1,4-Dilithio-1, 3-butadienes



tetramerization of arylacetylenes to construct *trans*-tetraenes (Figure 1).[5c] Although many examples are known for the synthesis of *trans*-substituted octatetraenes,[4−6] there is no report in the literature for the synthesis of fully substituted *all*-*cis* octatetraenes, except for one case where they formed as byproducts.[7]

We have been working on the synthesis and synthetic applications of multiply substituted 1-lithio-1,3-butadienes (**I**, Scheme 1)[8] and 1,4-dilithio-1,3-butadienes (**III**).[9] The alkyl substituents on the butadienyl skeletons in **I** and **III** are *all*-*cis* oriented. Inspired by the formation of conjugated dienes via homocoupling of vinylic monocopper reagents,[10,11] we envisioned that the 1,3-butadienyl monocopper compounds (**II**), generated in situ from the reaction between **I** and CuCl, could undergo a similar thermal dimerization to provide a direct method to synthesize octaalkyl-substituted *all*-*cis* octatetraene derivatives **1**. However, the corresponding thermal dimerization did not occur. Interestingly, 1,4-dicopper-1,3-butadienes (**IV**),[12] generated in situ from the reaction between **III** and CuCl, were found to undergo thermal decomposition-linear dimerization, yielding the corresponding octatetraenyl dicopper (**V**). The addition of lithium iodide was found very effective for this thermal decomposition-linear dimerization process. Hydrolysis of **V** afforded octa-alkyl substituted all-*cis* octatetraene derivatives **1** in excellent yields. Subsequent Pd-catalyzed cross-coupling of **V** with halides

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Scheme 3. Cyclic Dimerization of Octatetraenyl Dicopper Intermediates

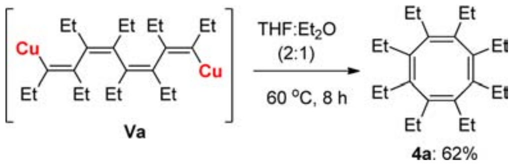
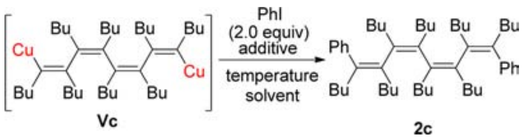


Table 1. Optimization of Reaction Conditions



entry	temp (°C)	time (h)	additive	solvent	yield of **2c**^{a} (%)
1	0	4		Et_2O	
2	0	4	DMPU	Et_2O	
3	rt	4		Et_2O	
4	rt	4	DMPU	Et_2O	
5	rt	4	$Pd(PPh_3)_4$ 5%	Et_2O	10
6	50	4	$Pd(PPh_3)_4$ 5%	THF/Et_2O (2:1)	42
7	60	8	$Pd(PPh_3)_4$ 5%	THF/Et_2O (2:1)	67
8	60	12	$Pd(PPh_3)_4$ 5%	THF/Et_2O (2:1)	64

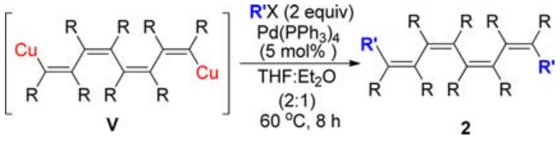
^{a} Isolated yields.

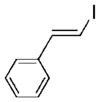
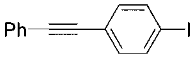
constructed fully substituted *all-cis* octatetraene derivatives **2**.

As demonstrated in Scheme 2, we first used the isolated purified 1,4-dilithio-1,3-butadiene **IIIa** as the starting material. However, only cyclic products **3a** and **4a** were observed. Surprisingly, when **IIIa** generated in situ from its corresponding 1,4-diiodo compounds **5a** was used,[13] the *all-cis*-substituted octaethyl 1,3,5,7-tetraene **1a** was obtained in 41% isolated yield, along with cyclic products **3a** and **4a**. The only difference between these two reactions was that in the second reaction 2 equiv of lithium iodide was generated in situ. This observation indicated that lithium iodide could promote the formation of the octatetraenyl dicopper **V** intermediates and stabilize them.

Thus, additional LiI was added. As expected (Scheme 2), when the dilithio compound **III** generated in situ was treated with copper(I) chloride and extra lithium iodide, the color of the mixture changed from yellow to dark brown immediately. The mixture was stirred at 0 °C for 4 h, and copper mirror was observed. During this process, thermal decomposition and linear dimerization proceeded smoothly to afford the proposed *all-cis*-alkyl-substituted octatetraenyl dicopper **V**. Quenching of **V** with aqueous 3 N HCl afforded their corresponding tetraenes **1** in excellent isolated yields, which represented an efficient synthesis of *all-cis*-alkyl-substituted octatetraenes.

Table 2. Construction of Fully Substituted *all-cis*-Octatetraenes



entry	R in **V**	R'X	yield of **2** (%)^a
1	Et	PhI	68 (**2a**)
2	Et		29 (**2b**)
3	Bu	Ph—≡—Br	35 (**2d**)
4	Bu		71 (**2e**)

^{a} Isolated yields.

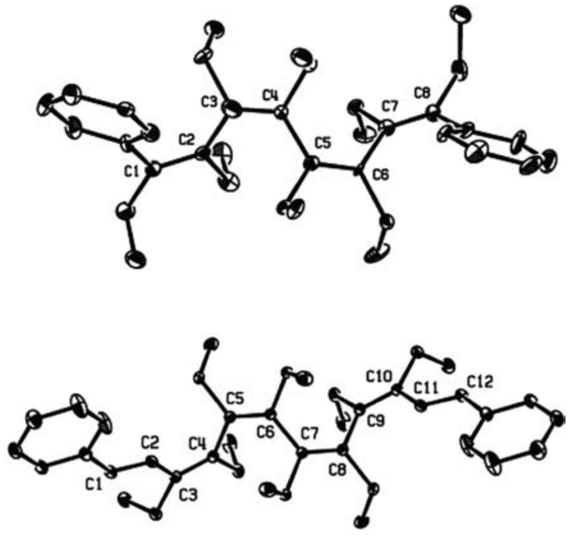


Figure 2. Single-crystal X-ray structures of **2a** (upper) and **2b** (down) with 20% thermal ellipsoids. Hydrogen atoms are omitted for clarity.

When the octatetraenyl dicopper **Va** generated in situ was heated at 60 °C for 8 h (Scheme 3), no obvious further linear dimerization took place. Instead, cyclic dimerization occurred, affording the octaethyl-substituted cyclooctatetraene **4a** as a major product in 62% isolated yield.[14]

Based on the above results, we envisioned that **V** could be further applied to introduce two more substituents via transition-metal-catalyzed cross-coupling reactions

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between the C−Cu bonds and electrophiles. Thus 1,8-double phenylation of **Vc** was first attempted (Table 1), aiming at the synthesis of 1,8-diphenyl octatetraene **2c**, which has an elongated π-conjugation. Optimal reaction conditions were realized as follows: $Pd(PPh_3)_4$ (5 mol %), in a mixed solvent (THF/Et_2O = 2: 1), 60 °C, 8 h. Under the optimal conditions (entry 7), the product **2c** was obtained in 67% isolated yield.

More examples of fully substituted *all*-*cis*-octatetraenes **2** are given in Table 2. In the cases of **2b** and **2d**, formation of their corresponding cyclooctatetraenes was also observed.

The reported computational studies have indicated that octatetraenes should exist in a nonplanar state.[15] Single-crystal X-ray structural analysis of **2a** and **2b** clearly show their all-*cis* and nonplanar skeleton structures (Figure 2).

In summary, an efficient synthesis of octaalkyl-substituted and decasubstituted *all*-*cis*-octatetraenes has been achieved via LiI-assiated thermal decomposition-linear dimerization of 1,4-dicopper-1,3-butadienes and subsequent Pd-catalyzed cross-coupling between C−Cu bonds and electrophiles. Further studies on a detailed reaction mechanism and synthetic applications are in progress.

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Supporting Information Available. Experimental details; X-ray data for **2a** (CCDC-911652) and **2b** (CCDC-911651); scanned NMR spectra of all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.