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Site-Selective Pd-Catalyzed Coupling of 1,4-Diiodo-1,3-alkadienes with Grignard Reagents and Its Application to the Synthesis of Fulvenes

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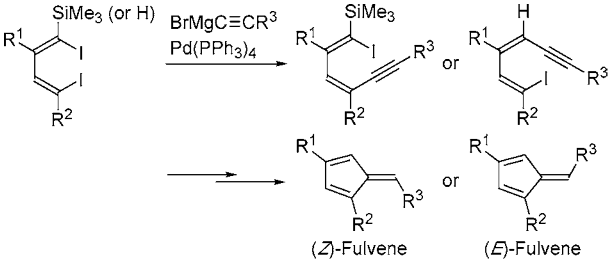
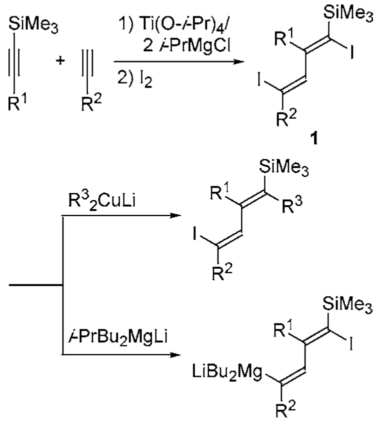
ABSTRACT



The coupling reaction of 1,4-diiodo-1,3-alkadienes with a Grignard reagent in the presence of a catalytic amount of $Pd(PPh_3)_4$ proceeded with excellent site-selectivity. Synthetic application of the reaction was demonstrated by a regio- and stereoselective synthesis of 1,3,6-trisubstituted fulvenes.

Recently, we have developed a one-pot method for synthesizing 1,4-diiodo-1,3-alkadienes of type **1** via regioselective coupling of 1-trimethylsilyl-1-alkynes and terminal alkynes by a divalent titanium reagent $Ti(O\text{-}i\text{-}Pr)_4/2i\text{-}PrMgCl$ and the following reaction of the resulting titanacyclopentadienes with I_2.[1] With an efficient and practical entry to **1** in hand, our next concern was their synthetic application by differentiating the reactivity of the two vinyliodo groups present in them. As shown in Scheme 1, we already reported that the reaction of **1** with organocuprate compounds proceeds with excellent site-selectivity by taking advantage of the presence of a silyl group at the α-position to the iodo group.[2] We also found that the iodine−magnesium exchange reaction of **1** with $i\text{-}PrBu_2MgLi$ proceeds with excellent site-selectivity at the vinyliodo moiety, which has no olefinic substituent at the β-position.[3]

Scheme 1



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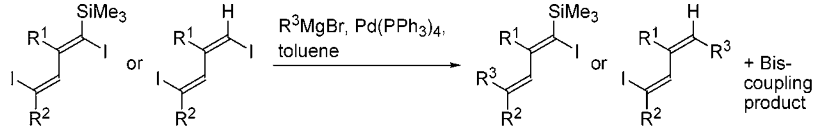
(1) (a) Yamaguchi, S.; Jin, R.-Z.; Tamao, K.; Sato, F. *J. Org. Chem.* **1998**, *63*, 10060−10062. (b) Hamada, T.; Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 7342−7344.

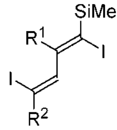
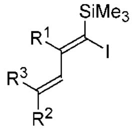
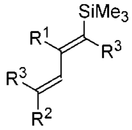
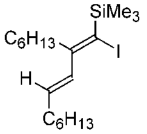
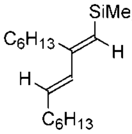
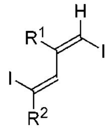
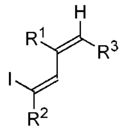
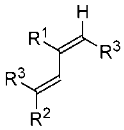
(2) Nakajima, R.; Delas, C.; Takayama, Y.; Sato, F. *Angew. Chem., Int. Ed.* **2002**, *41*, 3023−3025.

10.1021/ol0478032 CCC: $27.50

Table 1. Site-Selective Pd-Catalyzed Coupling Reaction of 1,4-Diiodo-1,3-alkadienes **1** or **2** with Grignard Reagents



1 **2**

entry	substrate			R^3MgBr[a]	product yield[b]		isolated yield of mono-coupling product (%)
	R^1	R^2			mono-coupling product	bis-coupling product	
							
1	C_6H_{13}	C_6H_{13}	**1a**	Me	60%	15%	—[c]
2				CH_2=CH-	67%	0%	66
3				Ph	49%	13%	32
4				$C_6H_{13}C{\equiv}C$-	**3** 61%	7%	56
5	C_6H_{13}	$SiMe_3$	**1b**	Me	46%	39%	—[c]
6			**1a**	Et	 37%	 12%	—[c]
							
7	C_6H_{13}	C_6H_{13}	**2a**[d]	Me	95%	0%	87
8				Et	93%	0%	61
9				CH_2=CH-	94%	0%	93
10				Ph	87%	4%	74
11				$C_6H_{13}C{\equiv}C$-	**4** 89%	8%	72
12				$THPO(CH_2)_3C{\equiv}C$-	**5** 80%	6%	64

[a] 1.5 and 1.1 equiv of R^3MgBr was used for the reaction with **1** and **2**, respectively. [b] NMR yield. [c] Isolated yield was low, because separation of the mono- and bis-coupling products was difficult. [d] Compound **2a** was prepared in 76% yield by the reaction of **1a** with *n*-Bu_4NF in THF at −78 °C.

We have now found that the Pd-catalyzed coupling reaction of 1,4-diiodo-1,3-alkadienes with Grignard reagents[4] also proceeds with excellent selectivity. The results of the coupling reaction of **1** or their desilylated derivative **2**, obtained by treatment with *n*-Bu_4NF, are summarized in Table 1. It can be seen from Table 1 that the site-selective mono-coupling reaction of both **1** and **2** proceeded with methyl, vinyl, aryl, and alkynyl Grignard reagents in the presence of a catalytic amount of $Pd(PPh_3)_4$. Although an alkyl Grignard reagent having β-hydrogen such as an ethyl Grignard reagent also reacted selectively with **2** (entry 8), the reaction with **1** resulted in a protodeiodination reaction mainly (entry 6), presumably as a result of the sterically more hindered character of the vinyliodo moiety of **1**. In every case, another possible mono-coupling product, the site-isomer, was produced in less than 3% yield if any. Whereas the reaction with **2** proceeded smoothly by using 1.1 equiv of a Grignard reagent, that of **1** needed use of 1.5 equiv of the Grignard reagent to consume the starting **1** completely. Also, under these reaction conditions, the reaction with **1** also afforded some unidentified products as well as bis-coupling products, though the reaction with a vinyl and an alkynyl Grignard reagent gave the bis-coupling product in a rather small amount. It should be also noted that we confirmed that the bis-coupling product was not produced by further reaction of the possible site-isomer formed in situ, which was not observed, with the Grignard reagent (see Supporting Information).

The general trend of the site-selectivity of the reaction can be summarized as follows: The coupling reaction occurs at the sterically less hindered vinyl carbon preferentially since the reaction of **1** proceeded more readily at the vinyliodo moiety having an alkyl rather than that having a more congested trimethylsilyl group at the α-position, and compounds **2** reacted preferentially at the vinyliodo moiety without an α-substituent. If both substituents at the α-position to the iodo group are the same, the coupling reaction seems

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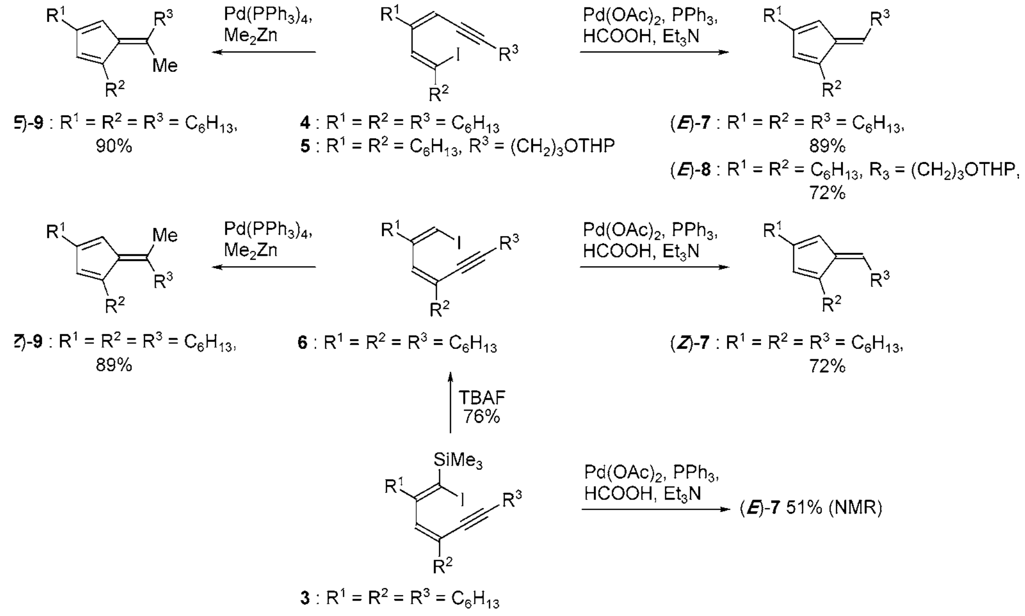
(3) Fukuhara, K.; Takayama, Y.; Sato, F. *J. Am. Chem. Soc.* **2003**, *125*, 6884−6885.

(4) Dang, H. P.; Linstrumelle, G. *Tetrahedron Lett.* **1978**, 191−194.

Scheme 2



to occur more easily at the vinyliodo moiety having a proton rather than an alkyl group at the β-position to the iodo group, as exemplified by the reaction shown in entry 5 in Table 1.

The present finding opens a new entry to a variety of 1-iodo-1,3-alkadienes that can be utilized as starting compounds for preparation of polysubstituted conjugated dienes[2] and cyclopentenones[5] using the reactivity of the vinyliodo moiety present in them.

Fulvenes serve as substrates for cycloaddition reaction by which useful organic compounds including natural products can be provided.[6] Fulvenes are also a class of compounds that have proven useful in metallocene synthesis.[7] The preparation of fulvenes, therefore, has long attracted much interest.[8] However, the preparation of poly-substituted fulvenes in a regio- and stereoselective manner is not necessarily an easy process, and the reported selective methods developed thus far allow preparation of some limited kinds of compounds.[8] Especially noteworthy is the fact that few selective methods have been developed that allow access to fulvenes having an exocyclic double bond with *Z*-configuration. We report herein that the compounds obtained by the coupling reaction of **1** and **2** with an alkynyl Grignard reagent can be readily converted to fulvenes, thus opening up a general selective preparation of 1,3,6-trisubstituted fulvenes including those having a *Z*-exocyclic double bond.[9]

Intramolecular carbopalladation[10] of **4** and **5** (shown in entries 11 and 12 in Table 1, respectively) with formic acid and Et$_3$N in the presence of catalytic amounts of Pd(OAc)$_2$ and PPh$_3$[11] produced the corresponding 1,3,6-trisubstituted fulvene with *E*-geometry, (*E*)-**7** and (*E*)-**8**, in excellent yield (Scheme 2). Meanwhile, the olefinic isomer of the former, (*Z*)-**7**, could be obtained from **3** (shown in entry 4 in Table 1) after converting to **6** by protodesilylation. Treatment of **4** and **6** with Me$_2$Zn in the presence of Pd(PPh$_3$)$_4$[12] provided the corresponding methylated fulvenes (*E*)-**9** and (*Z*)-**9**, which are mutually diastereomer. It should be noted that Pd-catalyzed reaction of **3** with formic acid and Et$_3$N afforded (*E*)-**7** instead of the expected silyl-containing fulvene or its desilylated product (*Z*)-**7** (Scheme 2). Further study to clarify the reaction mechanism of the formation of (*E*)-**7** from **3** is underway. Thus, a new general synthetic method for preparing fulvenes starting from three kinds of acetylenes is now opened up. Although Pd-catalyzed syntheses of poly-

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(5) Song, Q.; Li, Z.; Chen, J.; Wang, C.; Xi, Z. *Org. Lett.* **2002**, *4*, 4627−4629.

(6) For recent examples, see: (a) Barluenga, J.; Martínez, S.; Suárez-Sobrino, A. L.; Tomás, M. *J. Am. Chem. Soc.* **2002**, *124*, 5948−5949. (b) Nair, V.; Jayan, C. N.; Radhakrishnan, K. V.; Anilkumar, G.; Rath, N. P. *Tetrahedron* **2001**, *57*, 5807−5813. (c) Barluenga, J.; Martínez, S.; Suárez-Sobrino, A. L.; Tomás, M. *J. Am. Chem. Soc.* **2001**, *123*, 11113−11114.

(7) For recent examples, see: (a) Won, Y. C.; Kwon, H. Y.; Lee, B. Y.; Park, Y.-W. *J. Organomet. Chem.* **2003**, *677*, 133−139 and references therein. (b) Suzuka, T.; Ogasawara, M.; Hayashi, T. *J. Org. Chem.* **2002**, *67*, 3355−3359. (c) Döring, S.; Erker, G. *Synthesis* **2001**, 43−45.

(8) For reviews on the preparation of fulvenes, see: (a) Hafner, K. *Pure Appl. Chem.* **1990**, *62*, 531−540. (b) Yates, P. *Adv. Alicyclic Chem.* **1968**, *2*, 59−184. (c) Bergmann, E. D. *Chem. Rev.* **1968**, *68*, 41−84. (d) Day, J. H. *Chem. Rev.* **1953**, *53*, 167−189.

(9) For a selective synthesis of 1,3,6-trisubstituted fulvenes, see: ref 8 and (a) Kämpchen, T.; Moddelmog, G.; Schulz, D.; Seitz, G. *Liebigs Ann. Chem.* **1988**, 855−860. (b) Kasai, M.; Funamizu, M.; Fujita, K.; Kitahara, Y. *Chem. Lett.* **1975**, 297−300.

(10) For a general review, see: Cacchi, S.; Fabrizi, G. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; Wiley-Interscience: New York, 2002; Vol. 1, pp 1335−1359.

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(12) Oppolzer, W.; Pimm, A.; Stammen, B.; Hume, W. E. *Helv. Chim. Acta* **1997**, *80*, 623−639.

(13) (a) Dzhemilev, U. M.; Khusnutdinov, R. I.; Shchadneva, N. A.; Nefedov, O. M.; Tolstikov, G. A. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, 2360−2362. (b) Kim, H.-J.; Choi, N.-S.; Lee, S. W. *J. Organomet. Chem.* **2000**, *616*, 67−73. (c) Radhakrishnan, U.; Gevorgyan, V.; Yamamoto, Y. *Tetrahedron Lett.* **2000**, *41*, 1971−1974. (d) Kotora, M.; Matsumura, H.; Gao, G.; Takahashi, T. *Org. Lett.* **2001**, *3*, 3467−3470 and references therein.

substituted fulvenes starting from acetylenes have been reported, these methods make it possible to access only those having the same substituent.[13]

In conclusion, Pd-catalyzed coupling of 1,4-diiodo-1,3-alkadienes with Grignard reagents proceeded selectively at the less hindered vinylic carbon, thus providing a versatile new entry into 1-iodo-1,3-alkadienes. Synthetic application of this reaction was demonstrated by a regio- and stereoselective synthesis of 1,3,6-trisubstituted fulvenes. Further synthetic application of 1-iodo-1,3-alkadienes thus obtained is now in progress in our group.

Supporting Information Available: Experimental procedures and physical properties of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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