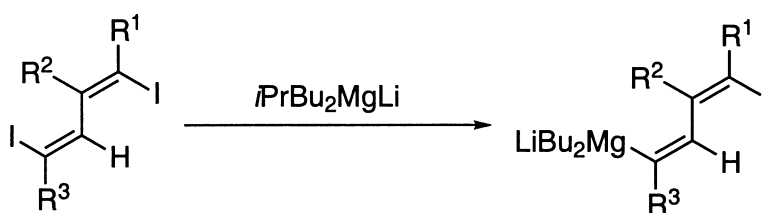


Site-Selective Iodine–Magnesium Exchange Reaction of 1,4-Diiodo-1,3-Alkadienes by an Organomagnesium Ate Complex, and Its Application to Synthesis of Polysubstituted Styrenes and Phenols

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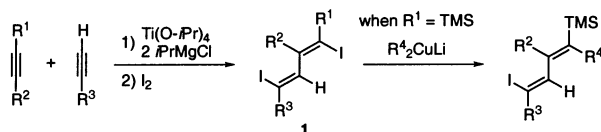
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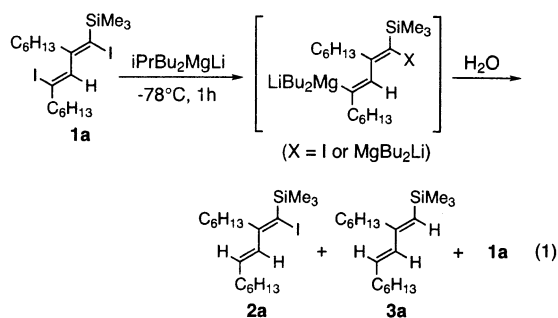
Recently, we have developed a one-pot method for synthesizing 1,4-diiodo-1,3-alkadienes **1** via regioselective coupling of internal and terminal acetylenes mediated by a divalent titanium reagent $\text{Ti}(\text{O}-i\text{-Pr})_4$ $i\text{-PrMgCl}$, and the following reaction of the resulting titanacyclopentadienes with I_2 .^{1–3} With an efficient and practical entry to **1** in hand, our next concern has been their synthetic utilization. We already reported that site-selective coupling of **1** with organocuprate compounds is possible by taking advantage of the presence of a silyl group at the α -position to the iodo group as shown in Scheme 1, thus providing a practical and efficient

Scheme 1. Synthesis of 1,4-Diiodo-1,3-Alkadienes **1** and Their Site-Selective Coupling with Cuprates



approach to a variety of 1-iodo-1,3-alkadienes.⁴ We have now found that site-selective iodine–magnesium exchange reaction of **1** can be attained using an organomagnesium ate complex, thus opening up another practical entry to 1-iodo-1,3-alkadienes.

The results of the reaction of **1a**, prepared from 1-trimethylsilyl-1-octyne and 1-octyne, with $i\text{-PrBu}_2\text{MgLi}$ ⁵ in THF at -78°C for 1 h are shown in eq 1. The reaction using 1 equiv. of $i\text{-PrBu}_2\text{MgLi}$

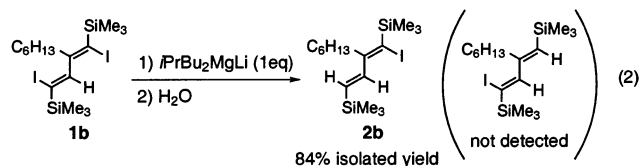


$i\text{-PrBu}_2\text{MgLi}$	yield (NMR)		
	2a	3a	1a
0.5eq	44%	0%	51%
1eq	90%	4%	<1%
2eq	76%	20%	0%

afforded, after hydrolysis, mono iodide **2a** exclusively in 90% yield (NMR analysis). The reaction using 0.5 equiv of $i\text{-PrBu}_2\text{MgLi}$ furnished an almost equal amount of **2a** and the starting **1a**. Meanwhile, use of 2 equiv of $i\text{-PrBu}_2\text{MgLi}$ provided dimagnesiated product **3a** in considerable amount; however, the major product was still **2a** and the yield of **3a** was 20%. In all of these reactions,

another possible monomagnesiated product, the site-isomer, was not detected. These results strongly indicated that iodine–magnesium exchange reaction of **1a** occurs more readily at the vinyliodo moiety connected with the hexyl group than that connected with the trimethylsilyl group, and also that the magnesium–iodine exchange of the resulting **2a** with $i\text{-PrBu}_2\text{MgLi}$ under these reaction conditions is rather slow.

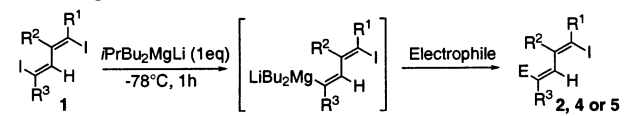
We first considered that this site-selectivity is owing to the difference in the substituent connected at the α -position to the iodo group in **1**, namely, the difference between a silyl and an alkyl group as is the case for the reaction shown in Scheme 1. However, the following experimental result indicated that the difference in reactivity is mainly due to whether there is an olefinic substituent at the β -position to the iodo group. Thus, as shown in eq 2, the



reaction of **1b** where both R^1 and R^3 are a Me_3Si group with 1 equiv of $i\text{-PrBu}_2\text{MgLi}$ provided monomagnesiated product **2b** highly predominantly, and again, another possible monomagnesiated compound was not detected.

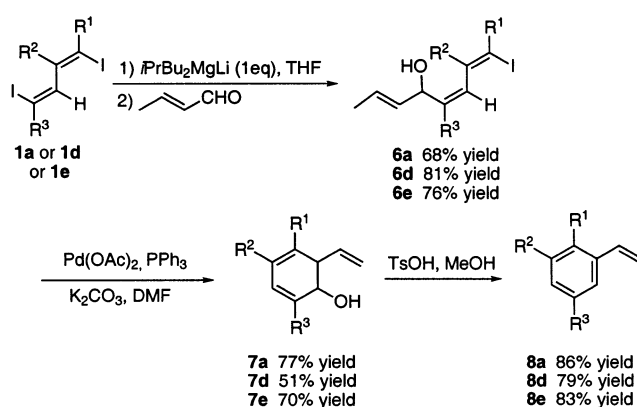
Although we do not at this time have a good explanation for the excellent site-selectivity observed here, it appears to be reasonably general, and additional results are collected in Table 1. Compound **1** in which both R^1 and R^3 are alkyl groups reacted with similar excellent selectivity as shown in entries 7 and 8. As shown in entry 6, alkyl chloride and benzyl ether survive under the reaction conditions so that monoiododienes **2** having such functionalities can be prepared readily. As can be seen from entries 2 and 3, the resulting magnesiated compounds could be trapped with electrophiles other than H_2O such as an aldehyde and allyl halide. It should also be noted that iodine–metal exchange reaction of **1** with $t\text{-BuLi}$ proceeded with similar site-selectivity; however, the degree of the selectivity did not reach a synthetically attractive level.⁶

1-Iodo-1,3-alkadienes have been used as synthetic intermediates for preparation of polysubstituted conjugated dienes,⁴ cyclopentenones,⁷ and pyridines⁸ using the reactivity of the vinyliodo moiety present in them. Thus, the present new efficient method to prepare 1-iodo-1,3-alkadienes might find utility for synthesizing a wide variety of such compounds. Moreover, the present reaction allows access to iododienes the preparation of which otherwise is difficult or requires multistep reaction sequences. Our concern was, therefore, the synthetic application of such dienes which can become readily available for the first time by the present reaction, and we

Table 1. Reaction of 1,4-Diiodo-1,3-Alkadienes **1** with *i*-PrBu₂MgLi^a


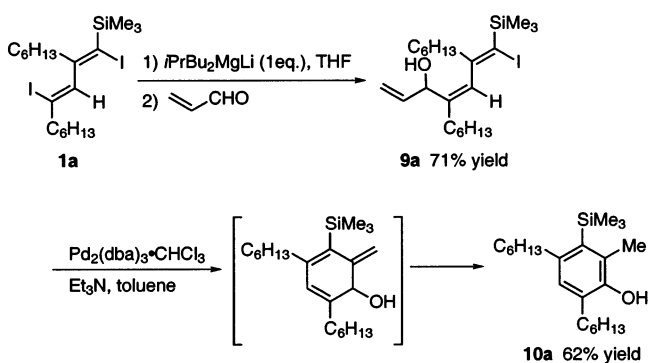
Entry	Compound 1			Electrophile	Isolated yield of product 2, 4 or 5 (%)	
	R ¹	R ²	R ³			
1	1a	SiMe ₃	C ₆ H ₁₃	H ₂ O	2a (E = H) 83	
2				CH ₂ =CHBr ^b	4a (E = CH ₂ =CHCH ₂ -) 83	
3				PhCHO	5a (E = PhCH(OH)-) 68	
4	1b	SiMe ₃	C ₆ H ₁₃	H ₂ O	2b (E = H) 84	
5	1c	SiMe ₃	C ₆ H ₁₃	<i>c</i> -C ₆ H ₁₁	2c (E = H) 79	
6	1d	SiMe ₃	-(CH ₂) ₃ Cl	-(CH ₂) ₂ OBn	H ₂ O	2d (E = H) 89
7	1e	C ₃ H ₇	C ₃ H ₇	C ₃ H ₇	H ₂ O	2e (E = H) 86
8 ^c	1f	-(CH ₂) ₁₀ ^c	<i>c</i> -C ₆ H ₁₁	H ₂ O	2f (E = H) 76	

^a All reactions were carried out using 0.2 mmol of **1** and 0.2 mmol of *i*-PrBu₂MgLi in THF (1 mL) unless otherwise noted. ^b CuCN·2LiCl (30 mol %, 0.06 mmol) was added. ^c 1.5 equiv (0.3 mmol) of *i*-PrBu₂MgLi was used.

Scheme 2. Synthesis of 2,3,5-Trisubstituted Styrenes via Intramolecular Heck Reaction of **6**

have now succeeded in opening up an efficient method for synthesizing polysubstituted styrenes and phenols.

Compound **6** prepared by the reaction with crotyl aldehyde after the reaction of **1** with *i*-PrBu₂MgLi could be converted into the corresponding styrene via a two-step reaction. Thus, as shown in Scheme 2, intramolecular Heck reaction⁹ of **6a** proceeded smoothly providing **7a** in 77% yield, which, in turn, was converted into styrene derivative **8a** in 86% yield by treatment with TsOH in methanol. Similarly, styrenes **8d** and **8e** were prepared in good overall yield from **6d** and **6e**, respectively. It should be noted that polysubstituted styrenes are useful intermediates and important structural constituents in organic and polymer chemistry. When the regioselective alignment of the substituents on the styrene ring is considered, their synthesis becomes more and more difficult with an increase in the number of substituents.¹⁰ The present synthetic method which opens up an efficient and general entry to 2,3,5-

Scheme 3. Synthesis of 2-Methyl-3,4,6-trisubstituted Phenols by the Intramolecular Heck Reaction of **9**

trisubstituted styrenes having a variety of substituents, therefore, might find wide utility.

It is also noteworthy that 2-methyl-3,4,6-trisubstituted phenols,¹¹ which seem rather difficult to access, can be readily prepared from **1**. Thus, Heck reaction of **9** obtained from **1** and acrolein provided phenols **10** presumably via the corresponding *o*-isotoluene¹² intermediate as exemplified by the preparation of **10a** as shown in Scheme 3.

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Supporting Information Available: Experimental procedures, physical properties of products, and a proposed reaction course (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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