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Synthesis and Applications of 1-Iodo-4-MgCl-1,3-dienes and 1-Iodovinyl Phenylmagnesium Chlorides

Junnian Wei,[a] Yongliang Zhang,[a] Wen-Xiong Zhang[a] and Zhenfeng Xi[a,b]

Selective I/Mg exchange reactions of 1,4-diiodo-1,3-dienes and *o*-iodo-2-(2-iodovinyl)benzenes were achieved via *i*PrMgCl•LiCl. Various 1-iodo-4-MgCl-1,3-dienes and 1-iodovinyl phenylmagnesium chlorides were thus efficiently generated and synthetically applied to afford new C-C bonds via reactions of the alkenyl or aryl C-MgCl bonds with different electrophiles. Useful conjugated compounds including polysubstituted benzenes, naphthalenes and phosphine compounds could be synthesized readily via further applications of the remaining alkenyl C-I bonds and subsequent cyclization reactions.

Introduction

Dihalo compounds such as **1a** and **1b** (Scheme 1) have become readily available.[1] From such dibromides or diiodides, their corresponding organo-di-metallic compounds (reagents), including 1,4-dilithio-1,3-dienes,[2] 1,4-dicopper-1,3-dienes[3] and 1,4-dimagsia-1,3-dienes,[4] can be easily generated (**Model I**, Scheme 1). Reaction chemistry study of these organo-di-metallic reagents has demonstrated unique and useful synthetic applications because of the cooperative effect of the two C-M bonds in the same molecule.[2-5] Conceptually, if one of the two C-X bonds could be selectively metalated, compounds containing one C-X bond and one C-M bond in the same molecule would be generated (**Model II**, Scheme 1). Useful synthetic applications of such compounds can be thus expected because the C-X bond and the C-M bond will react with totally different reagents. For example, the C-M bond will react with various electrophiles while the C-X bond can be applied to numerous cross-coupling reactions.

The halogen/metal exchange reaction is a general and important strategy to prepare organometallic reagents.[6] To realize the above-mentioned selective mono-metallation reaction, we first tried to get 1-lithio-4-iodo-1,3-dienes via mono-lithiation of 1,4-diiodo-1,3-dienes **1a** with organolithium reagents. However, the selectivity of such I/Li exchange reaction was not satisfactory. In addition to the expected 1-lithio-4-iodo-1,3-dienes, 1,4-dilithio-1,3-dienes were always generated in nonnegligible amounts. And a rather low reaction temperature was required in this reaction. We then considered to try other milder halogen/metal exchange reactions. In 2003, Sato *et al*. reported a site-selective I/Mg exchange reaction of 1,4-diiodo-1,3-dienes using an organomagnesium ate complex (Scheme 1).[7] In 2004, Knochel *et al*. reported a LiCl-mediated Br/Mg exchange reaction to prepare functionalized aryl compounds from organic bromides under mild conditions.[8] This method greatly promoted the accessibility of functionalized Grignard reagents in organic synthesis.[9] Motivated by Sato and Knochel's pioneering work, herein we report a selective mono I/Mg exchange reaction of 1,4-diiodo-1,3-dienes (**1a**) and *o*-iodo-2-(2-iodovinyl)benzenes (**1b**) via *i*PrMgCl•LiCl (Knochel reagent). Various 1-

iodo-4-MgCl-1,3-dienes and 1-iodovinyl phenylmagnesium chlorides were thus efficiently generated and synthetically applied.
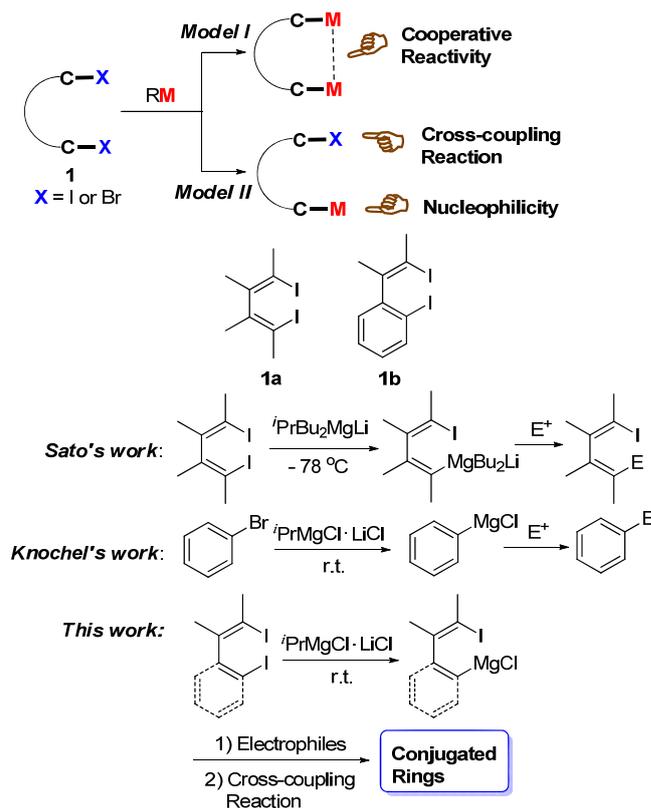
Scheme 1. Halogen/metal exchange reactions of dihalo compounds.

Results and Discussion

Selective mono I/Mg exchange reactions of 1,4-diiodo-1,3-dienes (1a) and *o*-iodo-2-(2-iodovinyl)benzenes (1b): We first chose the tetraethyl 1,4-diiodo-1,3-diene **1a1** to react with *i*PrMgCl•LiCl in THF at room temperature. Results are shown in Scheme 2. It was found that this mono I/Mg exchange reaction could selectively afford the desired 1-iodo-4-magnesia-1,3-diene **Ia**, which upon hydrolysis gave its corresponding mono iodide **2a1**. The undesired dimagnesia-1,3-diene **IIa** was not generated in most cases. With 1 or 2 equivalents of the Knochel reagent, compound **2a1** could be obtained in moderate to good yeilds, but remarkable amounts of diiodide **1a1** remained unreacted, even after 6 h (entry 4). This observation indicated that this I/Mg exchange reaction was slow. With 4 equivalents of *i*PrMgCl•LiCl, the reaction completed after 6 h, affording the product **2a1** in 75% isolated yield after hydrolysis (entry 6).
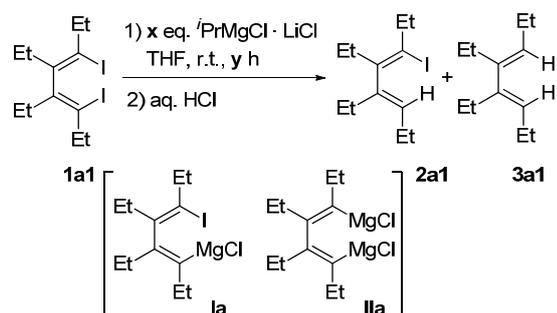
entry	x	y	Yield (%)[a]		
			2a1	**3a1**	**1a1**
1	1.0	1	26	0	69
2	2.0	1	39	0	55
3	2.0	3	65	<5	28
4	2.0	6	67	<5	25
5	4.0	1	72	0	24
6	4.0	6	95(75)	<5	<1

[a] GC yields. Isolated yields are given in parentheses.

Scheme 2. I/Mg exchange reaction conditions of 1,4-diiodo-1,3-diene **1a1**.
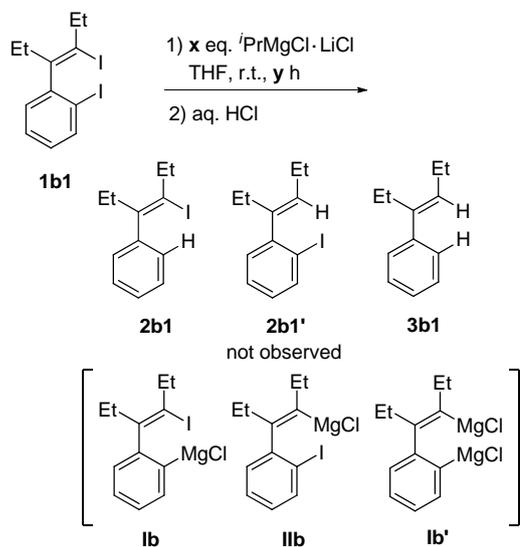
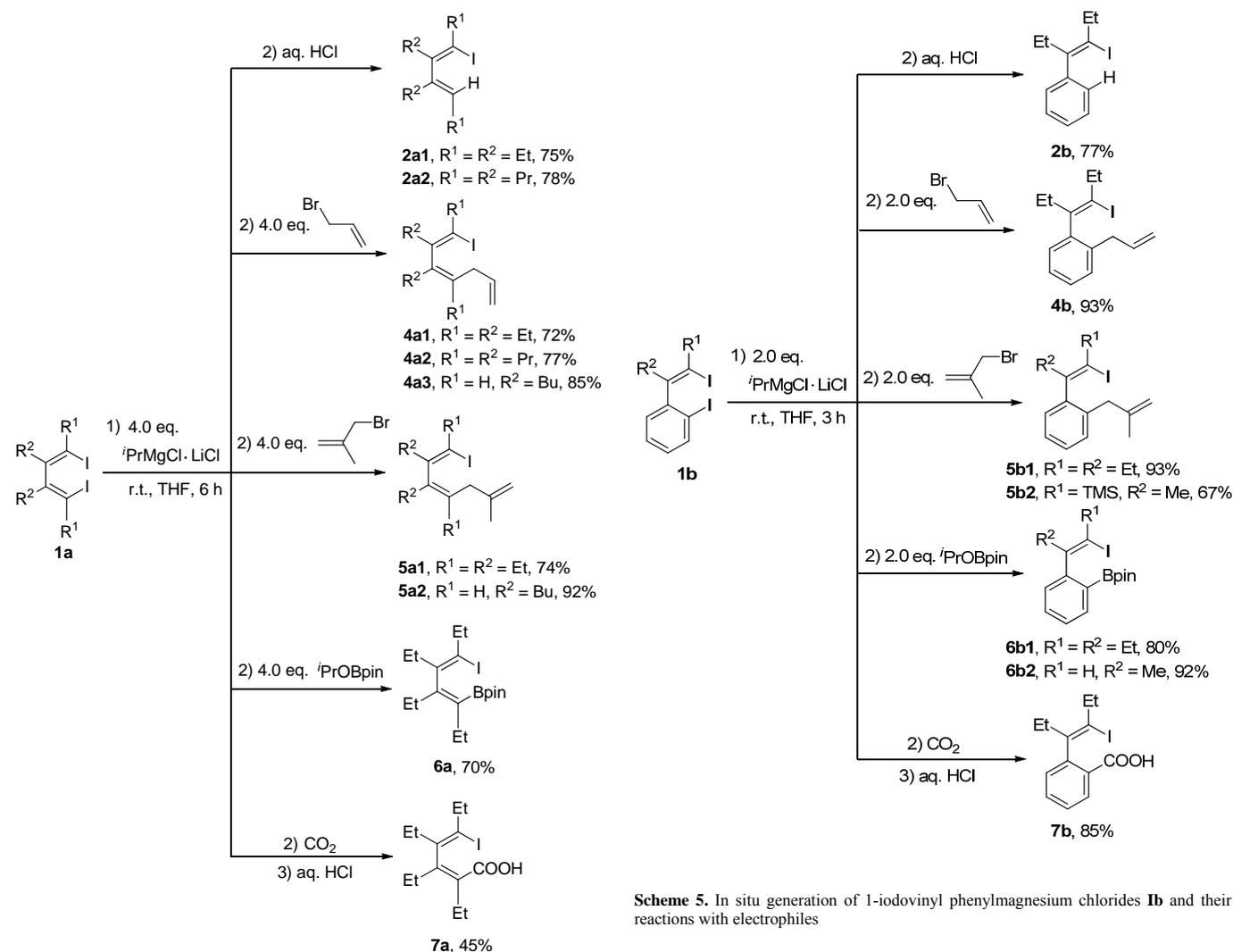
entry	x	y	2b1	3b1	1b1
1	1.0	1	35	0	62
2	2.0	1	65	0	33
3	2.0	3	95(77)	<5	<1

[a] GC yields. Isolated yields are given in parentheses.

Scheme 3. I/Mg exchange reaction conditions of *o*-iodo-2-(2-iodovinyl)benzene **1b1**.

For the I/Mg exchange reaction of *o*-iodo-2-(2-iodovinyl)benzenes **1b** with the Knochel reagent, the exchange reaction rate was found to be faster than that of 1,4-diiodo-1,3-dienes **1a**. As shown in Scheme 3, the I/Mg exchange reaction of **1b1** with the Knochel reagent would generate **Ib**, **Ib'** and **IIb**. However, no formation of the product **2b1'** was detected in all cases, which indicated that the alkenyl C-I bond did not undergo the I/Mg exchange reaction. The aryl C-I bond was selectively magnesiated. This high selectivity is probably because the aryl C-I bond is more reactive than the alkenyl C-I bond in the I/Mg exchange reaction and the possible transition state is considered resembling hypervalent halogen complex, for which aryl ring could provide more stabilization to the transition state than alkenyl via delocalization of the charge on halogen.[9] With 2 equivalents of *i*PrMgCl•LiCl, the reaction of **1b1** completed after 3 h, affording the product **2b1** in 77% isolated yield after hydrolysis.

2a1, $R^1 = R^2 = Et$, 75%
2a2, $R^1 = R^2 = Pr$, 78%

4a1, $R^1 = R^2 = Et$, 72%
4a2, $R^1 = R^2 = Pr$, 77%
4a3, $R^1 = H$, $R^2 = Bu$, 85%

5a1, $R^1 = R^2 = Et$, 74%
5a2, $R^1 = H$, $R^2 = Bu$, 92%

6a, 70%

7a, 45%

Scheme 4. In situ generation of 1-iodo-4-magnesia-1,3-dienes **Ia** and their reactions with electrophiles

2b, 77%

4b, 93%

5b1, $R^1 = R^2 = Et$, 93%
5b2, $R^1 = TMS$, $R^2 = Me$, 67%

6b1, $R^1 = R^2 = Et$, 80%
**6b2**, $R^1 = H$, $R^2 = Me$, 92%

7b, 85%

Scheme 5. In situ generation of 1-iodovinyl phenylmagnesium chlorides **Ib** and their reactions with electrophiles

Reactions of in situ generated 1-iodo-4-MgCl-1,3-dienes Ia and 1-iodovinyl phenylmagnesium chlorides Ib with electrophiles: New C-C bonds were highly efficiently generated when the in situ generated 1-iodo-4-MgCl-1,3-dienes **Ia** and 1-iodovinyl phenylmagnesium chlorides **Ib** were treated with electrophiles, such as allyl bromide and carbon dioxide (Schemes 4 and 5). In addition, the C-MgCl bond could be easily transformed to the C-B bond in high yields when treated with isopropoxyboronic acid pinacol ester.

Intramolecular Heck reaction of 1-iodo-1,3-diene analogues: As shown in Scheme 6, 1-iodo-1,3-butadiene analogues **4a** and **5a** were tested in the intramolecular Heck reaction.[10] Pentasubstituted benzenes **8a** were obtained in high yields via a intramolecular Heck reaction and a subsequent aromatization step. For **5a** with an extra methyl group in the allyl unit, cycloheptatriene products **9a**, other than the benzene-type products **8a**, were generate in high yields. Cycloheptatrienes are useful and structurally interesting compounds.[11] This synthetic method offered a new way to build such polysubstituted cycloheptatrienes.
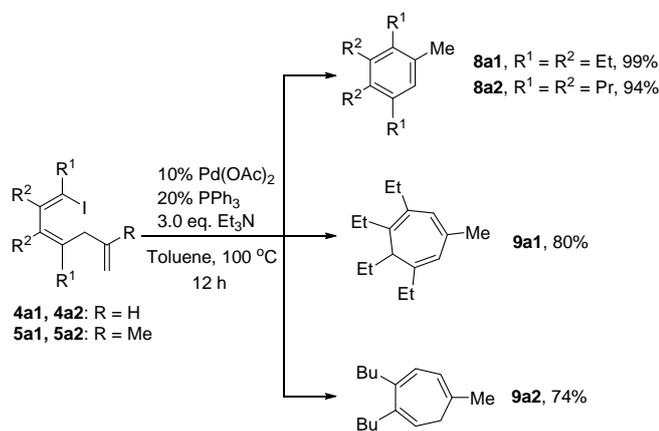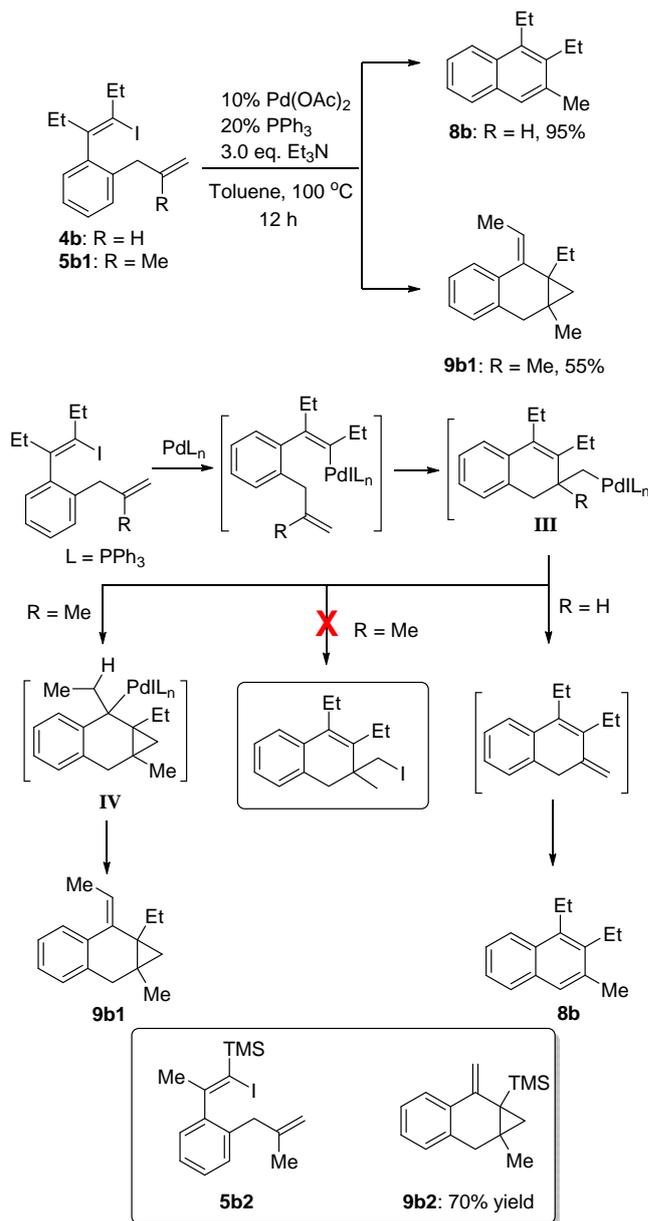
Scheme 6. Intramolecular Heck reaction of allyl 1-iodo-1,3-diene derivatives.

As given in Scheme 7, compound **4b** could also be converted into their corresponding polysubstituted naphthalenes **8b** readily in high yields via a similar intramolecular Heck reaction and a subsequent aromatization step. It should be noted that these polysubstituted benzenes **8a** and naphthalenes **8b** are very difficult to synthesize by other methods.[12] However, when we chose the compound **5b1** with an extra methyl group to go through this Heck reaction under the same condition, a novel compound **9b1** containing a bicyclo[4.1.0] ring was obtained in a moderate yield (Scheme 7). Similarly, when the compound **5b2** was used, the product **9b2** was obtained in 70 isolated yield.

A proposed mechanism is shown in Scheme 7. After the oxidative addition of palladium and the subsequent intramolecular alkene insertion, the pivotal intermediate **III** was generated. When intermediate **III** had a β-hydrogen atom (R = H), the β-hydride elimination could happen to give naphthalene product **8b** after aromatization. When there was no β-hydrogen atom (R = Me) in intermediate **III**, no β-hydride elimination could happen. In this situation, the intermediate **III** would go through the second intramolecular alkene insertion to offer the intermediate **IV**. Since the intermediate **IV** had syn-β hydrogens, thus the subsequent β-hydride elimination of **IV** would happen and lead to the final products **9b1**. Recently, reductive elimination of alkyl halides from alkylpalladium halide species without β-hydrogens has attracted much attention.[13,14] However, in our cases (R = Me), no corresponding C(sp³)–I reductive elimination product was observed, indicating that the intramolecular alkene insertion was more favored than C(sp³)–I reductive elimination.

Synthesis of functionalized phosphine compound starting from 1-iodo-1,3-diene analogues: As further demonstration of the synthetic utility of designed compounds containing one C-I bond and one C-M bond in the same molecule, we synthesized the phosphine compound **10** from **6b2** and Ph₂PH in 73% isolated yield (Scheme 8). The structure of **10** was confirmed by single crystal X-ray structural analysis (Figure 1).

Scheme 7. Intramolecular Heck reaction of allyl 2-iodovinylbenzene derivatives.
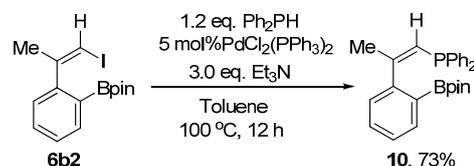
Scheme 8. Synthesis of phosphine ligands.
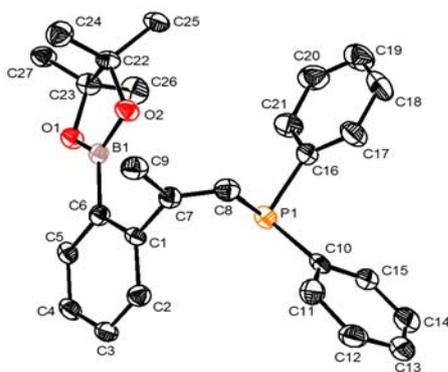
Figure 1. ORTEP drawings of **10** with 30% thermal ellipsoids. Hydrogen atoms are omitted for clarity.

Conclusions

In summary, we have reported herein the I/Mg exchange reactions of 1,4-diiodo-1,3-dienes **1a** and *o*-iodo-2-(2-iodovinyl)benzenes **1b** and their synthetic applications. The reactions efficiently afforded diverse 1-iodo-4-magnesia-1,3-dienes and 1-iodovinyl phenylmagnesium chlorides in situ. After quenched with different electrophiles, various functionalized derivatives were obtained. Most of the reactions were under mild conditions. By taking advantage of the rich reactivity of the derivatives, useful conjugated compounds including polysubstituted benzenes, naphthalenes and phosphine compounds could be synthesized readily via the subsequent cross-coupling reactions.

Acknowledgements

Notes and references

[a] Mr. J. Wei, Mr. Y. Zhang, Prof. Dr. W.–X. Zhang, Prof. Dr. Z. Xi Beijing National Laboratory for Molecular Sciences, Key Laboratory of Bioorganic Chemistry and Molecular Engineering of Ministry of Education, College of Chemistry, Peking University, Beijing 100871 (China). E-mail: zfxi@pku.edu.cn

[b] Prof. Dr. Z. Xi State Key Laboratory of Organometallic Chemistry Shanghai Institute of Organic Chemistry, Shanghai 200032 (China).

† Electronic Supplementary Information (ESI) available: General information, experimental procedures, characterization data, copies of ^{1}H NMR and ^{13}C NMR spectra, and crystal data of compound **10** (CCDC-1011067). For ESI and crystallographic data in CIF or other electronic format, see DOI: 10.1039/b000000x/

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