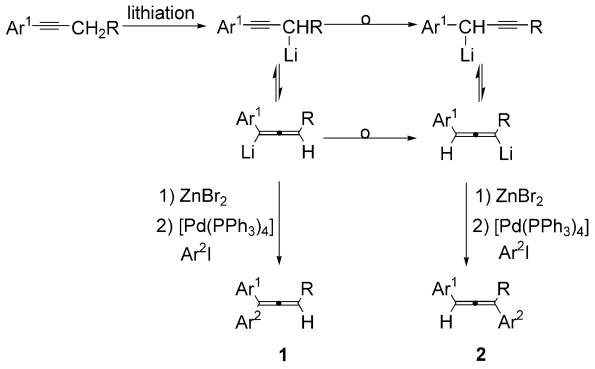
Li Reactions in Organic Synthesis

A 1,3-Lithium Shift of Propargylic/Allenylic Lithium and the Subsequent Transmetalation Coupling Reaction with Aryl Halides**

Shengming Ma and Qiwen He*

Selective synthesis has been a formidable challenge in organic synthesis, especially controlled highly selective synthesis beginning from the same starting materials.[1] Herein, we report a novel clean 1,3-lithium shift reaction of propargylic/allenylic lithium (Scheme 1). Based on this observation, the corresponding sequential transmetalation and Pd-catalyzed coupling with aryl halides leading to 1,1-diarylallenes (**1**) or 1,3-diarylallenes (**2**) highly selectively from the same 1-aryl-1-alkynes has been developed (Scheme 1).

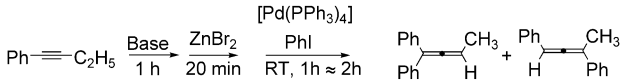


Scheme 1. Protocol for the selective synthesis of 1,1-diarylallenes or 1,3-diarylallenes by monolithiation of 1-aryl-1-alkynes, transmetalation, and Pd-catalyzed coupling with aryl halides.

Recently, we developed a monolithiation reaction of 1-aryl-1-alkynes with or without the mediation of $HgCl_2$.[2,3] The propargylic/allenylic lithium formed in this reaction undergoes sequential transmetalation and Pd-catalyzed coupling with organic halides leading to alkynes or allenes depending on the structures of the starting materials.[4] Quite recently, however, we observed that the sequential monolithiation of 1-aryl-1-alkynes beyond 1-aryl-1-propyne, (1-phenyl-1-butyne), the transmetalation, Pd-catalyzed coupling reaction with aryl halides when conducted by different chemists, or even the same chemist at different times, surprisingly gave two products. These products were identified as allenes **1a** and **2a** and formed in very different ratios ranging from 0:100 to 100:0; in other words, in terms of the ratio of **1a** to **2a**, the results were difficult to reproduce (entries 1 and 2, Table 1).

Further investigations showed that with different lithiation reagents, the ratios of **1a** and **2a** are also different, some of the representative results are summarized in Table 1 with the following noteworthy points: (1) No lithiation was observed with *n*BuLi or *t*BuLi at −78 °C (entry 7, Table 1);

Table 1: The effect of base on the lithiation of 1-aryl-1-butyne, transmetalation, and the Pd-catalyzed coupling with phenyl iodide.



1a **2a**

Entry	*T*[a]	Yield[b] (**1a**/**2a**) *n*BuLi	*t*BuLi	LDA
1	8 °C	100:0–0:100	100:0–0:100	84%[c] (0:100)
2	−10 °C	100:0–0:100	54% (89:11)	–
3	−20 °C	70% (100:0)	28% (93:7)	98% (0:100)
4	−40 °C	54% (100:0)	54% (100:0)	96% (19:81)
5	−55 °C	–	–	94% (45:55)
6	−65 °C	–	–	88% (77:23)
7	−78 °C	no lithiation	no lithiation	50% (91:9)

[a] Lithiation temperature. [b] NMR yield determined with CH_2Br_2 as the internal standard. [c] Yield of the isolated product.

[*] Prof. S. Ma, Ms. Q. He
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
354 Fenglin Lu, Shanghai 200032 (P. R. China)
Fax: (+86) 21-6416-7510
E-mail: masm@mail.sioc.ac.cn

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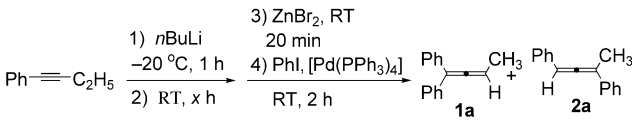
(2) Lithiation with LDA at −78 °C followed by transmetalation and coupling afforded **1a** and **2a** in 50% yield with a ratio of 91:9 (entry 7, Table 1). Lithiation with LDA at a higher temperature favors the formation of **2a**; (3) lithiation with *n*BuLi or *t*BuLi at −20 °C or −40 °C led to the highly selective or exclusive formation of the nonisomerized product **1a** (entries 3 and 4, Table 1). These facts indicate that the temperature and amine may be the factors that control the isomerization of 1-aryl-1-alkyn-3-yl or 1-aryl-1,2-alkadien-1-yl lithium to 1-aryl-2-alkyn-1-yl or 1-aryl-1,2-alkadien-3-yl lithium, respectively (Scheme 1).

In fact, it was observed that when the lithiation of 1-phenyl-1-butyne was conducted at −20 °C for 1 h then at room temperature for 2 h, instead of 1,1-diphenyl-1,2-butadiene (**1a**), the sequential reaction afforded 1,3-diphenyl-1,2-butadiene (**2a**) in 74% yield (Scheme 2). With a longer

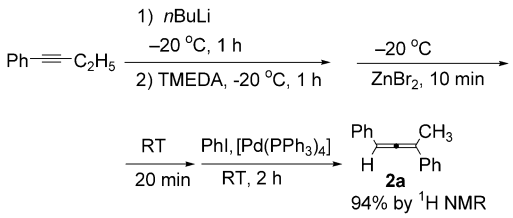


x (h)	yield by ^{1}H-NMR (%) (**1a**/**2a**)
1	90 (29:71)
2	74 (<1:99)
5	10 (0:100)
> 11	unidentified mixture

Scheme 2. Different lithiation conditions gave different ratios of **1a**/**2a**.

reaction time for the lithiation at room temperature, the yields of **1a** and **2a** decreased dramatically. When the lithiation was performed at −20 °C for 1 h followed by the addition of *N*,*N*,*N*′,*N*′-tetramethyl ethylene diamine (TMEDA) at −20 °C, the same sequential reaction also afforded the isomerized product 1,3-diphenyl-1,2-butadiene (**2a**) in 94% yield, thus indicating an interesting effect of amine on the 1,3-lithium shift (Scheme 3).

Through trial and error, we were happy to identify two suitable sets of reaction conditions: A) lithiation at −20 °C with *n*BuLi for 1 h followed by transmetalation ($ZnBr_2$ was added at −20 °C followed by stirring at room temperature) and coupling at room temperature for the selective formation of 1,1-diarylallenes; B) lithiation at room temperature with LDA for 1 h followed by transmetalation and coupling at room temperature for the selective formation of 1,3-diarylallenes. Under conditions A and B, the results can be easily reproduced. Some typical results are presented in Table 2, which indicates that: 1) the reaction is general for differently substituted 1-aryl-1-alkynes/aryl halides; 2) the regioselectivity for the formation of 1,1-diarylallenes and 1,3-diarylallenes is excellent.



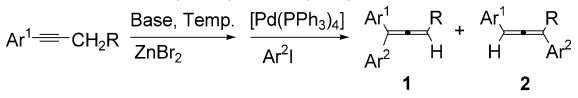
Scheme 3. The effect of TMEDA on the 1,3-lithium shift.

In conclusion, we have observed a clean and complete 1,3-lithium shift reaction of 1-aryl-1-alkyn-3-yl or 1-aryl-1,2-alkadien-1-yl lithium leading to 1-aryl-1,2-alkadien-3-yl or 1-aryl-2-alkyn-1-yl lithium, respectively. Although this kind of 1,3-metal shift has been observed,[5–7] the present protocol provides a clear-cut control of the lithiation as well as the isomerization. Under conditions A and B, 1,1-diarylallenes and 1,3-diarylallenes, respectively, can be prepared starting from the same alkynes. Although the mechanism of 1,3-lithium shift is not clear, this work may open up a new area for the study and control of 1,3-metal shifts in propargyl/allenylic species. Further investigations in this area are continuing in our laboratory.

Experimental Section

Typical procedure (conditions A): *n*BuLi (0.45 mL, 1.6 M in hexanes, 0.72 mmol) was added to a solution of 1-phenyl-1-butyne (78 mg, 0.6 mmol) in THF (3 mL) in a dry Schlenk tube at −20 °C under N_2. The reaction mixture was stirred at −20 °C for 1 h, then a solution of dry $ZnBr_2$ (275 mg, 1.2 mmol) in THF (4 mL) was added. After a further 10 min at this temperature the reaction mixture was warmed up to room temperature and kept there for 20 min. $[Pd(PPh_3)_4]$ (35 mg, 5 mol%) and iodobenzene (83 μL, 0.72 mmol) were subsequently added, and the resulting mixture was stirred at room

Table 2: Reaction under conditions A (*n*BuLi) and B (LDA)



Entry (**1**/**2**)	Ar^1	CH_2R	Ar^2I	Base	*T* [°C]	Yield [%][a]
1	Ph	C_2H_5	C_6H_5I	*n*BuLi	−20	55 (**1a**:**2a** = 100:0)
2	Ph	C_2H_5	C_6H_5I	LDA	8	84 (**1a**:**2a** = 0:100)
3	Ph	C_4H_9	C_6H_5I	*n*BuLi	−20	71 (**1b**:**2b** = 99:1)
4	Ph	C_4H_9	C_6H_5I	LDA	10	89 (**1b**:**2b** = 0:100)
5	Ph	C_4H_9	*p*-MeC_6H_4I	*n*BuLi	−20	79 (**1c**:**2c** = 99:1)
6	Ph	C_4H_9	*p*-MeC_6H_4I	LDA	20	99 (**1c**:**2c** = 0:100)
7	Ph	C_4H_9	α-$C_{10}H_8I$	*n*BuLi	−20	63 (**1d**:**2d** = 100:0)
8	Ph	C_4H_9	α-$C_{10}H_8I$	LDA	20	56 (**1d**:**2d** = 0:100)
9	Ph	C_4H_9	*p*-$MeOC_6H_4I$	*n*BuLi	−20	74 (**1e**:**2e** = 98:2)
10	Ph	C_4H_9	*p*-$MeOC_6H_4I$	LDA	30	83 (**1e**:**2e** = 0:100)
11	Ph	C_4H_9	*p*-$MeO_2CC_6H_4I$	*n*BuLi	−20	93 (**1f**:**2f** = 100:0)
12	Ph	C_4H_9	*p*-$MeO_2CC_6H_4I$	LDA	19	71 (**1f**:**2f** = 0:100)
13	Ph	C_3H_7	C_6H_5I	*n*BuLi	−20	76 (**1g**:**2g** = 100:0)
14	Ph	C_3H_7	C_6H_5I	LDA	11	96[b] (**1g**:**2g** = 0:100)
15	*p*-PhC_6H_4	C_3H_7	C_6H_5I	*n*BuLi	−20	77 (**1h**:**2h** = 100:0)
16	*p*-PhC_6H_4	C_3H_7	C_6H_5I	LDA	18	72 (**1h**:**2h** = 0:100)

[a] Yield of isolated products with the ratios determined by 300 MHz ^{1}H NMR analysis. [b] NMR yield determined with CH_2Br_2 as the internal standard.

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temperature. After the reaction was complete, as monitored by TLC (eluent: petroleum ether, 60–90 °C), it was quenched with saturated NH_4Cl and extracted with ether. The product solution was dried over $MgSO_4$, the solvent was removed by rotary evaporation, and the crude product was purified by flash chromatography on silica gel (petroleum ether) to afford **1a**[8] (68 mg, 55 %) as a liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.43$–7.25 (m, 10 H), 5.72 (q, $J = 7.1$ Hz, 1 H), 1.89 ppm (d, $J = 7.1$ Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): $\delta =$ 206.32, 137.24, 128.42, 128.28, 126.98, 109.18, 88.85, 14.33 ppm; MS (70 eV): *m*/*z* (%): 206 (84.30) [M^+], 191 (100) [$M^+ - CH_3$]; IR (neat): $\tilde{\nu} = 1943\ cm^{-1}$; HRMS calcd for $C_{16}H_{14}$ [M^+]: 206.10955, found: 206.10914.

Typical procedure (conditions B)**:** LDA (0.4 mL, 2.0 M in THF/ethylbenzene/pentane, 0.8 mmol) was added to a solution of 1-phenyl-1-butyne (58 mg, 0.45 mmol) in THF (3 mL) in a dry Schlenk tube at room temperature under N_2. After the solution had been stirred for 1 h at room temperature, a solution of dry $ZnBr_2$ (499 mg, 2.22 mmol) in THF (4 mL) was added. After a further 25 min at this temperature, [$Pd(PPh_3)_4$] (22 mg, 5 mol %) and iodobenzene (42 μL, 0.38 mmol) were added. After the reaction was complete as monitored by TLC (eluent: petroleum ether, 60–90 °C), it was quenched with saturated NH_4Cl and extracted with ether. The resulting solution was dried over $MgSO_4$, the solvent was removed by rotary evaporation, and the crude product was purified by flash chromatography on silica gel (petroleum ether) to afford **1b**[9] (65 mg, 84 %) as a liquid. ^{1}H NMR ($CDCl_3$, 300 MHz): $\delta = 7.53$–7.47 (m, 2 H), 7.40–7.20 (m, 8 H), 6.50 (q, $J = 2.7$ Hz, 1 H), 2.25 ppm (d, $J = 2.7$ Hz, 3 H); ^{13}C NMR ($CDCl_3$, 75.4 MHz): $\delta = 206.77$, 136.23, 134.44, 128.67, 128.43, 127.01, 126.99, 126.85, 125.78, 104.48, 96.56, 16.75 ppm; MS (70 eV): *m*/*z* (%): 206 (79.98) [M^+], 191 (100) [$M^+ - CH_3$]; IR (neat): $\tilde{\nu} = 1936\ cm^{-1}$.

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Keywords: allenes · cross-coupling · isomerization · lithiation · palladium

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