ORGANIC
LETTERS

2008
Vol. 10, No. 8
1521−1523

Highly Regioselective Synthesis of Trisubstituted Allenes via Lithiation of 1-Aryl-3-alkylpropadiene, Subsequent Transmetalation, and Pd-Catalyzed Negishi Coupling Reaction

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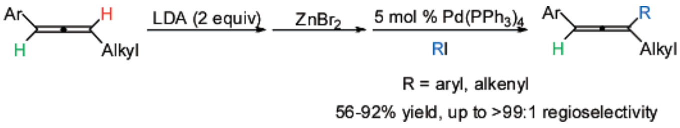
Received January 26, 2008

ABSTRACT



A novel methodology for the synthesis of trisubstituted allenes is reported. Lithiation of 1-aryl-3-alkylpropadienes and subsequent transmetalation with zinc bromide followed by Pd-catalyzed Negishi coupling reactions with halides afforded the corresponding trisubstituted allenes in a highly regioselective fashion with moderate to excellent yields. A plausible regioselective lithiation mechanism was proposed on the basis of deuterium labeling experiments.

Selectivity control has always been a challenge in organic synthesis.[1] Traditionally, the transition-metal-catalyzed cross-coupling reaction involving propargyl/1,2-allenyl species is one of the most important tools in the synthesis of allenes.[2] However, there is, in principle, a regioselectivity issue for this transformation. The ratio of allene/alkyne in the products usually depends on many factors including steric and electronic properties of the transition metals, ligands, and substrates, etc.[3] The propargyl/1,2-allenyl metal species usually exist in an equilibrium in the solution,[4] which is the intrinsic reason for the regioselectivity. Recently, during the

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(1) (a) Trost B. M., Fleming, I. Eds. *Comprehensive Organic Synthesis: Selectivity, Strategy and Efficiency in Modern Organic Chemistry*; Pergamon Press: Oxford, 1991. (b) Ward, R. S., Ed. *Selectivity in Organic Synthesis*; John Wiley: Chichester, 1999.

(2) For a review, see: Stang, P.; Diederich, F. Eds *Metal Catalyzed Cross Coupling Reactions*; VCH: Weinheim, 1998. For a handbook of the reactivity of organozinc reagents in organic synthesis, see: Knochel, P., Jones, P., Eds. *Organozinc Reagents: a Practical Approach*; Oxford University Press: New York, 1999. For a recent monograph on the preparation and reactivity of propargyl/allenyl zinc species, see: Rappoport Z., Marek, I., Eds. *The Chemistry of Organozinc Compounds*; John Wiley & Sons: Haifa, 2006, Chapter 10. For reviews on the cross-coupling reactions involving propargyl/1,2-allenyl metal species, see: Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589. Ma, S. *Eur. J. Org. Chem.* **2004**, 1175 and references cited therein. For some early references involving the cross coupling of propargyl/1,2-allenylpalladium species with organozinc species, see: Ruitenburg, T.; Kleijn, H; Elservier, C. J.; Vermeer, P. *Tetrahedron Lett.* **1981**, *22*, 1451. Elservier, C. J.; Mooiweer, H. H.; Kleijn, H.; Vermeer, P. *Tetrahedron Lett.* **1984**, *25*, 5571.

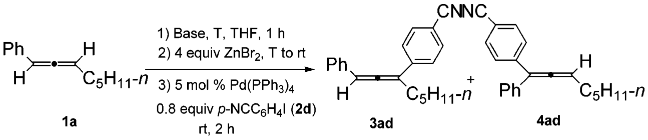
(3) (a) Colas, Y.; Cazes, B.; Gore, J. *Tetrahedron Lett.* **1984**, *25*, 845. (b) Tsuji, J.; Sujiura, T.; Yuhara, M.; Minami, I. *J. Chem. Soc., Chem. Commun.* **1986**, 922. (c) Mandai, T.; Matsumoto, T.; Kawada, M.; Tsuji, J. *Tetrahedron Lett.* **1993**, *34*, 2161. (d) Mandai, T.; Matsumoto, T.; Tsujiguchi, Y.; Matsuoka, S.; Tsuji, J. *J. Organomet. Chem.* **1994**, *473*, 343. (e) Radinov, R.; Hutchings, S. D. *Tetrahedron Lett.* **1999**, *40*, 8955. (f) Ma, S.; Wang, G. *Angew. Chem., Int. Ed.* **2003**, *42*, 4215. (g) Ma, S.; Zhang, A. *J. Org. Chem.* **1998**, *63*, 9601. (h) Ma, S.; Zhang, A. *J. Org. Chem.* **2000**, *65*, 2287. (i) Ma, S.; Zhang, A. *J. Org. Chem.* **2002**, *67*, 2287. For some selected recent examples, see: (j) Kjellgren, J.; Sundén, H.; Szabó, K. J. *J. Am. Chem. Soc.* **2004**, *126*, 474. (k) Zimmermann, M.; Wibbeling, B.; Hoppe, D. *Synthesis* **2004**, 765. (l) Hayashi, T.; Tokunaga, N.; Inoue, K. *Org. Lett.* **2004**, *6*, 305.

10.1021/ol8001909 CCC: $40.75

course of study on the cross coupling of propargyl/allenylzinc species with aryl halides, we have observed a controlled 1,3-lithium/hydrogen exchange and subsequent highly regioselective synthesis of trisubstituted allenes starting from lithiation of 1-phenyl-1-alkynes.[5] In this paper, we wish to report a highly regioselective synthesis of trisubstituted allenes from lithiation of 1-phenyl-1,2-alkadienes,[6] transmetalation, and the subsequent Negishi coupling with aryl and alkenyl halides.

After some screening, it was quite interesting to observe that the lithiation of 1-phenyl-1,2-octadiene with LDA followed by transmetalation with $ZnBr_2$ and $Pd(PPh_3)_4$-catalyzed cross coupling with phenyl iodide afforded 1-phenyl-3-(4-cyanophenyl)octa-1,2-diene (**3ad**) highly regioselectively (entry 1, Table 1).[7] Based on this observation, we screened the reaction conditions (Table 1). It is apparent that an excess amount of LDA is essential for the achievement of high yields. Reducing the amount of LDA led to lower yields but still high regioselectivities (entries 2 and 3, Table 1). Lithiation at −78 °C with 2 equiv of LDA gave similar results. Using *n*-BuLi as the lithiation reagent, higher yield was achieved, but the regioselectivity dropped to 96:4 (entry 5, Table 2). As a compromise between yield and selectivity, entry 1 was chosen as the standard conditions for this transformation.

Table 1. Effects of Base and Temperature on the Related Reaction of **1**a

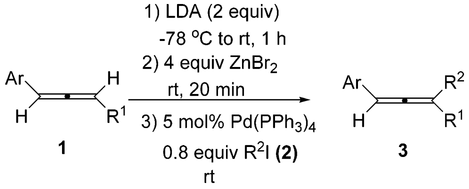


entry	base (equiv)	lithiation temp (°C)	yield of **3ad**[a] (%)	ratio of **3ad/4ad**[b]
1	LDA (2.0)	−78−24	84	>98:2
2	LDA (1.5)	−78−24	71	>99:1
3	LDA (1.2)	−78−24	25	>99:1
4	LDA (2.0)	−78[c]	67	>99:1
5	*n*-BuLi (2.0)	−78−24	88	96:4

[a] NMR yields using dibromomethane as the internal standard based on iodide used. [b] Determined by the NMR analysis of crude products. [c] Both lithiation and transmetalation were carried out at −78 °C, and then the reaction mixture was warmed to room temperature.

With the optimized reaction conditions in hand, the scope of this reaction was examined, and the results are summarized in Table 2. A broad range of functionality on R^2 is readily compatible with the optimized reaction conditions due to the mild nature of zinc reagents.[8] Both electron-donating (entries 6, 9, and 15, Table 2) and electron-withdrawing (entries 1, 4, 7, 14, and 16, Table 2) group substituted aryl iodides gave satisfactory yields. Steric effects of R^2 do not seriously influence the cross coupling since the cross coupling with 1-iodonaphthalene **2h** afforded the corresponding allene **3bh** in 57% yield (entry 11, Table 2). The reaction with alkenyl iodides **2i−k** proceeded efficiently at 0 °C to afford the corresponding vinylallenes **3bi**, **3aj**, and **3ak** in moderate to good yields (entries 11−13, Table 2). Electronic properties on the substrates seem to have some effects on the conversion, since for the reaction of 1-(4-methoxylphenyl)nona-1,2-diene **1c**, aryl iodide **2a** could not be fully consumed (entry 14, Table 2). It is noteworthy that bromine or fluorine atoms on the aryl iodide could be well tolerated (entries 2, 3 and 8, Table 2).

Table 2. Lithiation of 1-Aryl-1,2-alkadienes, Transmetalation, and Subsequent Pd-Catalyzed Cross-Coupling Reaction with Iodides[a]



entry	**1**		R^2	yield of
	Ar	R^1		**3**[b] (%)
1	Ph	*n*-C_5H_{11} (**1a**)	*p*-$MeO_2CC_6H_4$ (**2a**)	75 (**3aa**)
2	Ph	*n*-C_5H_{11} (**1a**)	*p*-BrC_6H_4 (**2b**)	79 (**3ab**)
3	Ph	*n*-C_5H_{11}(**1a**)	*p*-FC_6H_4 (**2c**)	73 (**3ac**)
4	Ph	*n*-C_5H_{11}(**1a**)	*p*-NCC_6H_4(**2d**)	68 (**3ad**)
5	Ph	*n*-C_6H_{13} (**1b**)	Ph(**2e**)	92 (**3be**)
6	Ph	*n*-C_6H_{13} (**1b**)	*p*-$MeOC_6H_4$ (**2f**)	79 (**3bf**)
7	Ph	*n*-C_6H_{13} (**1b**)	*p*-$MeO_2CC_6H_4$ (**2a**)	86 (**3ba**)
8	Ph	*n*-C_6H_{13} (**1b**)	*p*-BrC_6H_4 (**2b**)	84 (**3bb**)
9	Ph	*n*-C_6H_{13} (**1b**)	*m*-MeC_6H_4 (**2g**)	82 (**3bg**)
10	Ph	*n*-C_6H_{13} (**1b**)	α-Naphthyl (**2h**)	57 (**3bh**)
11	Ph	*n*-C_6H_{13} (**1b**)	(*E*)-*n*-$BuCH{=}CH_2$ (**2i**)	56[c] (**3bi**)
12	Ph	*n*-C_5H_{11} (**1a**)	(*E*)-$C_6H_4CH{=}CH_2$ (**2j**)	71[c] (**3aj**)
13	Ph	*n*-C_5H_{11} (**1a**)	(*E*)-$C_6H_{13}CH{=}CH_2$ (**2k**)	68[c] (**3ak**)
14	*p*-$MeOC_6H_4$	*n*-C_6H_{13} (**1c**)	*p*-$MeO_2CC_6H_4$ (**2a**)	78[d] (**3ca**)
15	*p*-$MeOC_6H_4$	*n*-C_6H_{13} (**1c**)	*p*-$MeOC_6H_4$ (**2f**)	80 (**3cf**)
16	*p*-MeC_6H_4	*n*-C_6H_{13}(**1d**)	*p*-NCC_6H_4 (**2d**)	81[e] (**3dd**)

[a] Unless otherwise noted, allene (0.5 mmol), LDA (1.0 mmol), $ZnBr_2$ (2.0 mmol), $Pd(PPh_3)_4$ (0.020 mmol), and iodides (0.4 mmol) were used in the reaction. [b] Isolated yields based on iodides used. [c] The cross-coupling reaction was conducted at 0 °C overnight. [d] 0.3 mmol of iodide was used with 22% of aryl iodide being recovered. [e] 0.2 mmol of iodide was used.

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(4) (a) Li: Reich, H. J.; Holladay, J. E. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2365. (b) Zinc: see ref 3g,h. (c) In: Lee, P. H.; Kim, H.; Lee, K.; Kim, M.; Noh, K.; Kim, H.; Seomoon, D. *Angew. Chem., Int. Ed.* **2005**, *44*, 1840. (d) Sn: Yu, C.-M.; Yoon, S.-K.; Baek, K.; Lee, J.-Y. *Angew. Chem., Int. Ed.* **1998**, *37*, 2392. (e) Cr: Muller, T. J. J.; Ansorge, M.; Polborn, K. *Organometallics* **1999**, *18*, 3690. (f) Pt and Pd: Baize, M. W.; Blosser, P. W.; Plantevin, V.; Schimpff, D. G.; Gallucci, J. C.; Wojcicki, A. *Organometallics* **1996**, *15*, 164.

(5) Ma, S.; He, Q. *Angew. Chem., Int. Ed.* **2004**, *43*, 988.

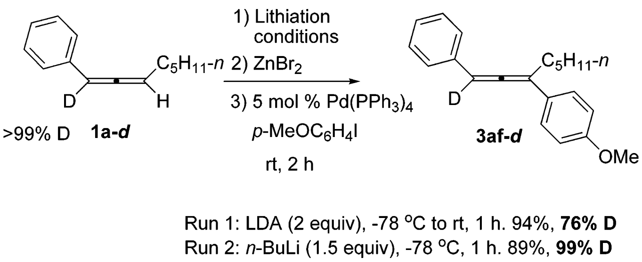
(6) For pioneering studies on the lithiation of simple allenes, see: (a) Michelot, D.; Linstrumelle, G. *J. Chem. Soc., Chem. Commun.* **1975**, 561. (b) Clinet, J.-C.; Linstrumelle, G. *Synthesis* **1981**, 875.

(7) The assignment of the regioselectivity was based on the distinct coupling constant of the two different allenic hydrogens.

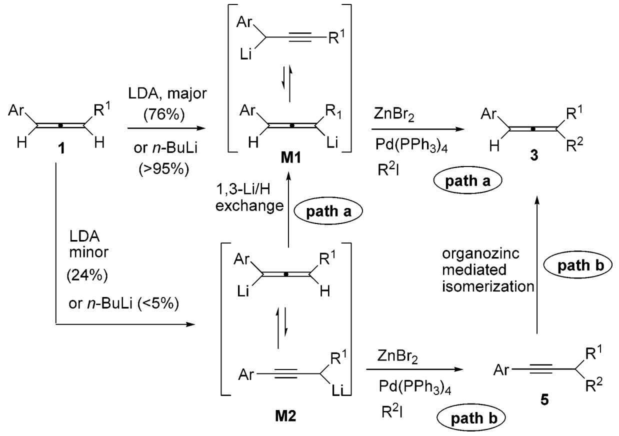
(8) Negishi, E.; Qian, M.; Zeng, F.; Anastasia, L.; Babinski, D. *Org. Lett.* **2003**, *5*, 1597.

To have a clear understanding of the mechanism of this process, 1-deuterated-1-phenylocta-1,2-diene **1a-*d*** was synthesized and subjected to the standard reaction conditions. It was found that the deuterium incorporation in the product **3af-*d*** dropped from >99% to 76% (run 1, Scheme 1). These results imply that with LDA as the base a direct regioselective lithiation is the major pathway (76%) leading to the 1-phenyl-1,2-octadien-3-yllithium intermediate **M1**, while about 24% of the allene was proposed to be lithiated at the 1-position to form the 1-phenyl-1,2-octadien-1-yl lithium intermediate **M2**, which may undergo 1,3-lithium/hydrogen exchange to form 1-phenyl-1,2-octadien-3-yl lithium intermediate **M1**.[5] Subsequent transmetalation and Pd-catalyzed cross coupling afforded the final products (Scheme 2). However, if the substrate was lithiated with 1.5 equiv of *n*-BuLi at −78 °C (run 2, Scheme 1) before transmetalation and cross coupling, the deuteration ratio in the product could be almost intact and the regioisomeric product observed in entry 5 of Table 1 was not formed, indicating a highly regioselective lithiation at the 3-position probably due to the isotopic effect of the deuterium atom.

Scheme 1. Deuterium Labeling Experiments

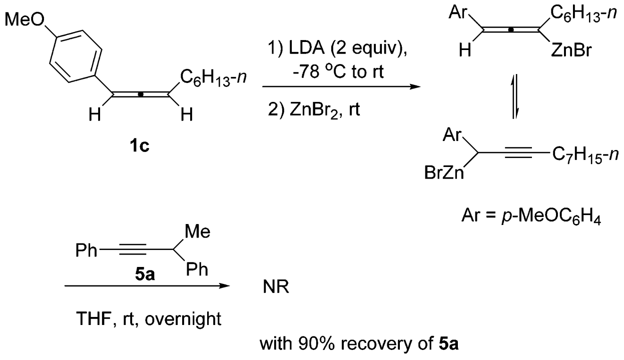


Scheme 2. Proposed Mechanism for the Lithiation of 1-Aryl-1,2-alkadienes and Subsequent Regioselective Synthesis of Trisubstituted Allenes



Besides the 1,3-lithium/hydrogen exchange mechanism (**path a**), an alternative mechanism, which involves the formation of alkyne derivative **5** and the subsequent isomerization to allene **3** (**path b**), was proposed to account for the deuterium loss under the conditions where LDA was used as the base (Scheme 2). To test the viability of **path b**, alkyne **5a** was prepared[9] and treated with 2 equiv of *n*-BuZnBr in THF at room temperature with no isomerization after 4 h. Furthermore, when **5a** was subjected to the propargyl/allenyl zinc species generated from **1c**, no reaction occurred with **5a** being recovered in 90% yield (Scheme 3). Meanwhile, a mixture was isolated and identified as the protonated mixture of propargyl/1,2-allenyl zinc species. This observation excludes the possibility of **path b**.

Scheme 3



In conclusion, we have reported a facile highly regioselective synthesis of trisubstituted allenes from the lithiation of 1-aryl-3-alkylpropadienes, transmetalation, and subsequent Pd-catalyzed Negishi coupling with aryl and alkenyl iodides. Further studies in this area are currently underway in our laboratory.

Acknowledgment. Financial support from National Natural Science Foundation of China (20732005 and 20423001), State Basic and Research Development Program (Grant No. 2006CB806105), and Shanghai Municipal Committee of Science and Technology are gratefully appreciated. We thank Mr. Ping Lu in our group for reproducing the results reported in entry 1, Table 1, and entries 1, 7, and 13, Table 2.

Supporting Information Available: Detailed experimental procedures and spectroscopic data for all compounds. This information is available free of charge via the Internet at http://pubs.acs.org.

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[9] Yasuda, M.; Saito, T.; Ueba, M.; Baba, A. *Angew. Chem. Int. Ed.* **2004**, *43*, 1414.