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Hydride reduction of *o*-(fluorosilyl)benzodifluorides for subsequent C–F transformations^{†‡}

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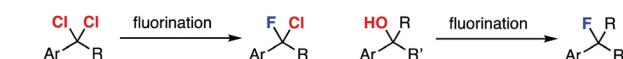
An efficient method for sequential C–F transformations of *o*-hydrosilyl-substituted benzotrifluorides is disclosed. A key to the success is hydride reduction of *o*-fluorosilyl-substituted difluoromethylenes prepared by a single C–F transformation of *o*-hydrosilyl-substituted benzotrifluorides. We succeeded in further C–F transformations via hydride abstraction of the resulting *o*-hydrosilyl group, enabling us to synthesize a wide variety of organofluorine compounds.

Organofluorine compounds are of great importance in broad research fields including pharmaceutical sciences, agrochemistry, and materials chemistry.¹ A wide variety of fluorinating reagents have been developed so far for synthesizing a wide range of organofluorines from halides and alcohols (Fig. 1A).² Despite the remarkable improvements in organofluorine chemistry enhancing the availability of organofluorines, it is not easy to synthesize highly functionalized benzyl fluoride derivatives due to the limited fluorination reactions.³

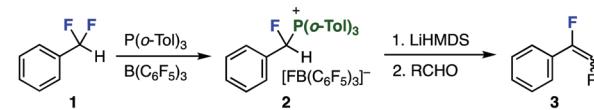
Modern studies of selective C–F transformations significantly expanded the accessibility of organofluorines (Fig. 1B and C).^{4,5} For example, in 2018, Young and coworkers succeeded in a single C–F transformation of α,α -difluorotoluene (**1**) with a frustrated Lewis pair between tri(*o*-tolyl)phosphine and tris(pentafluorophenyl)borane realizing facile synthesis of phosphonium salt **2**, which served in the preparation of fluoralkenes by the Wittig reaction with aldehydes (Fig. 1B).⁶ Our

recent achievements from 2016 on single C–F transformations of benzotrifluorides **4** enabled to synthesize difluoromethylenes **5** through hydride abstraction of *o*-hydrosilyl group (Fig. 1C).⁷ Herein, we disclose a new method to synthesize highly functionalized benzyl fluorides **8** from *o*-fluorosilyl-substituted difluoromethylenes **5** by C–F and C–Si transformations (Fig. 1D). A key to the success was efficient reconstruction of hydrosilyl group from fluorosilyl groups, which allowed

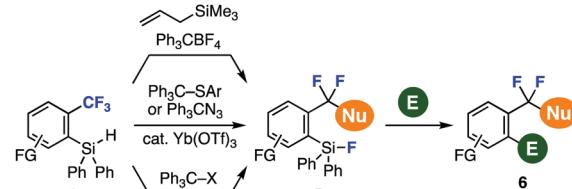
A Conventional approaches for synthesizing benzyl fluorides



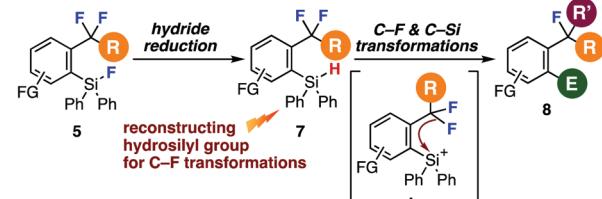
B Young's work



C Our previous works



D This work



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† Dedicated to Professor Koichi Narasaka with Gratitude on the Occasion of his 77th Birthday (Kiju).

‡ Electronic supplementary information (ESI) available: Experimental procedures, characterization for new compounds including NMR spectra. See DOI: 10.1039/d1cc06761c

Fig. 1 Backgrounds and an abstract of this study. (A) Conventional methods to synthesize benzyl fluorides. (B) Young's work. (C) Our previous studies. (D) This work.



Table 1 Screening of the reaction conditions

Entry	Hydride source	Yield (%)
1	LiAlH ₄	Quant ^a
2	NaBH ₄	0
3	i-Bu ₂ AlH	0
4	Li[i-Bu ₃ BH]	0
5	Li[Et ₃ BH]	0

^a Isolated yield (1.0 mmol scale).

further C–F transformations *via* silyl cation intermediate **I** generated by hydride abstraction.

First, we examined hydride reduction of *o*-fluorosilyl-substituted difluoromethylene **5a** using various metal hydrides (Table 1).⁸ As a result, *o*-hydrosilyl-substituted benzodifluoride **7a** was synthesized quantitatively with lithium aluminum hydride (LAH) without damaging labile difluoromethylene moiety⁸ and C–Si cleavage (entry 1). In sharp contrast, hydride reduction of fluorosilane **5a** resulted in failure when using sodium borohydride, diisobutylaluminum hydride, lithium triisobutylborohydride, or lithium triethylborohydride due to undesired decomposition (entries 2–5). The efficient LAH reduction of fluorosilane **7a** took place in 1.0 mmol scale, clearly showing the good scalability.

A wide range of *o*-fluorosilyl-substituted benzodifluorides **5** successfully participated in the hydride reduction to afford *o*-(hydrosilyl)benzodifluorides **7** (Fig. 2). For example, hydrosilanes

7b and **7c** having electron-rich thiienyl and electron-deficient 4-(trifluoromethyl)phenyl group, respectively, were efficiently prepared by LAH reduction. Hydride reduction furnishing bromo-substituted silane **7d** also proceeded smoothly leaving the bromo group untouched. The reduction of fluorodimethylsilyl group instead of fluorodiphenylsilyl group proceeded and required longer reaction time affording hydrosilane **7e** in good yield,⁹ where the dimethylsilyl group can serve in the C–F transformations.^{7a} Furthermore, efficient synthesis of **7f** bearing an acidic allylic proton was achieved without damaging difluoromethylene moiety. We succeeded in the preparation of difluorobenzyl sulfide **7g** and chlorides **7h** and **7i** in good yields. Also, difluorobenzyl bromide **7j** was synthesized in moderate yield. Unfortunately, the synthesis of difluorobenzyl *p*-toluenesulfonate **7k** resulted in failure due to the labile sulfonate ester moiety.

The reconstructed hydrosilyl group of difluoromethylenes served in further C–F transformations (Fig. 3). Indeed, single C–F chlorination of difluoromethylene **7a** with trityl chloride in chlorobenzene and 1,1,1,3,3-hexafluoro-2-propanol (HFIP)¹⁰ through benzyl cation intermediate **II** proceeded efficiently to afford highly functionalized benzyl fluoride **8a** in good yield (Fig. 3A).^{7c} Various benzyl fluorides **8b**–**8e** were synthesized through single C–F transformations of difluoromethylenes **7a**–**7d** having a range of functional groups (Fig. 3B). For instance, C–F chlorination products **8b**–**8d** were prepared from **7b**–**7d** with trityl chloride in moderate to good yields without damaging a wide variety of functionalities such as fluoro, chloro, allyl, fluorosilyl, trifluoromethyl, thiienyl, and bromo groups. It is worth noting that benzyl chloride **8c** was prepared selectively without C–F chlorination of trifluoromethyl group. Further C–F allylation of benzodifluoride **7a** also took place to afford **8e** in moderate yield.^{7a} When we attempted Yb-catalyzed C–F thiolation of benzodifluoride **7a** with 4-tolyl trityl sulfide,^{7b} benzyl fluoride **8f** was not obtained, showing the different reactivity of fluorobenzyl cation **II** generated from **7a** to difluorobenzyl cation intermediates in our previous reports.⁷ Owing to the great importance of organofluorine chemistry, successes in the synthesis of highly functionalized benzyl fluorides **8a**–**8e** obviously indicated the significant potential of sequential transformations *via* reconstruction of the hydrosilyl group.

Facile synthesis of α,α -difluorobenzyl chloride **7h** by a single C–F chlorination and subsequent LAH reduction was achieved from benzotrifluoride **4a** in a one-pot manner *via* removal of solvents under reduced pressure (Fig. 3C). Benzyl fluoride **8a** was prepared in good yield also from α,α -difluorobenzyl chloride **7h** by a single C–F allylation provably *via* α -chloro- α -fluorobenzyl cation **III**. Second C–F chlorination took place smoothly to provide α,α -dichlorobenzyl fluoride **8g** in moderate yield. Moreover, we succeeded in the preparation of benzyl fluoride **8a** from benzotrifluoride **4a** in a three-step, single purification procedure (Fig. 3D). Indeed, C–F allylation of **4a** followed by LAH reduction using the crude product and subsequent C–F chlorination provided benzyl fluoride **8a** in moderate yield.

Succeeding transformations of highly functionalized benzyl fluoride **8a** realized facile synthesis of organofluorines

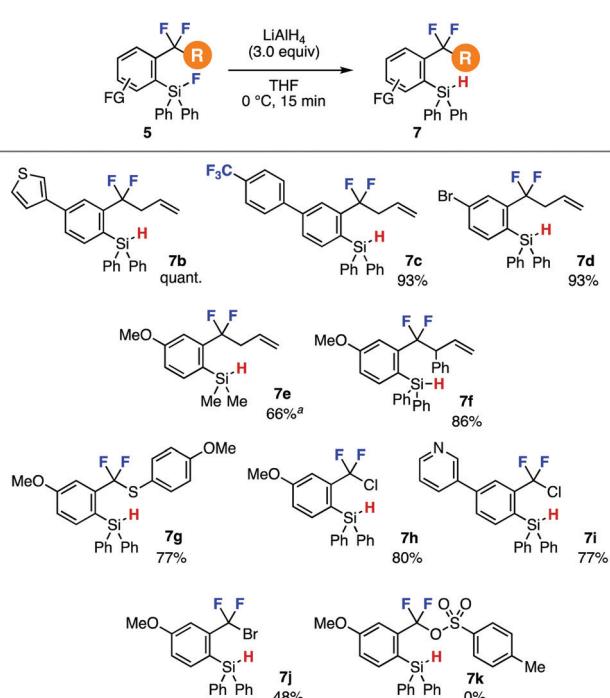


Fig. 2 Syntheses of *o*-(hydrosilyl)benzodifluorides **7**. See the ESI† for details. ^aThe reaction time was 2 h.



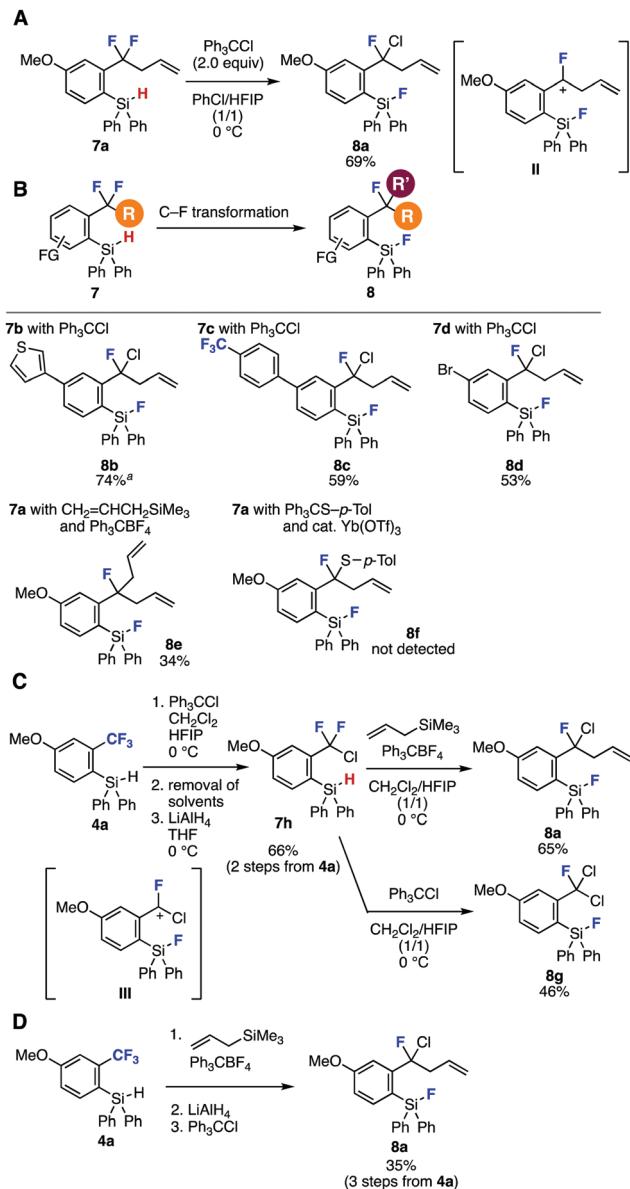


Fig. 3 Transformations of *o*-(hydrosilyl)benzodifluorides 7. See the ESI‡ for details. Isolated yields are shown otherwise noted. ^aNMR yield. (A) C–F chlorination of 7a. (B) Scope of benzyl fluoride synthesis. (C) Sequential C–F transformations of 4a via difluorobenzyl chloride 7h. (D) C–F transformations of 4a with a single silica-gel column chromatography purification.

involving 1-aryl-1-fluoro-1,3-butadiene 10a (Fig. 4A). For example, silver mediated C–Si bromination¹¹ of fluorosilane 8a furnished bromide 9a in moderate yields leaving various reactive functional groups intact (Fig. 4A, upper). Treatment of 9a with cesium carbonate in dimethyl sulfoxide (DMSO) at 120 °C provided 1,3-butadiene 10a in high yield with good *Z* selectivity.¹² Although 1,3-butadiene 10a was found to be labile under various conditions such as acidic or basic aqueous conditions, it is worthy to note that 1,3-butadiene 10a was synthesized by heating 9a in DMSO in the presence of cesium carbonate in high yield.¹³ In contrast, no diene formation was observed when boiling benzyl fluoride 9a in the presence of

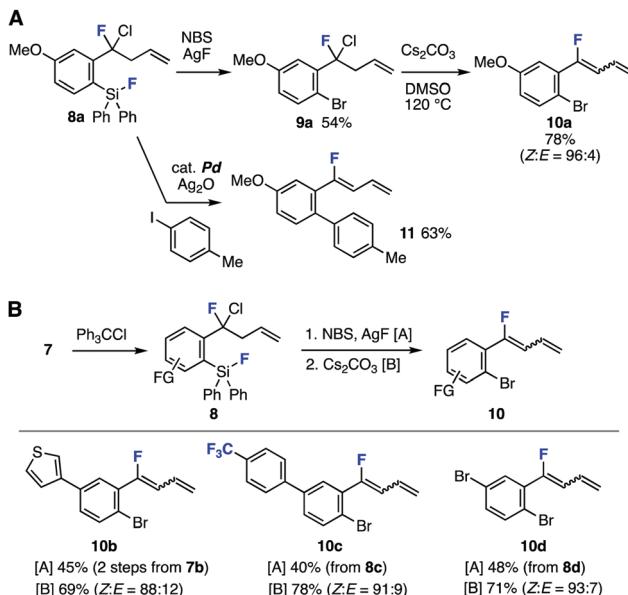


Fig. 4 Transformations of benzyl fluorides 8. (A) Synthesis of various organofluorines from 8a. (B) Fluorobutadiene synthesis.

cesium carbonate in toluene. When we treated *o*-fluorosilyl-substituted benzyl fluoride 8a with 4-iodotoluene in the presence of silver oxide and a catalytic amount of palladium catalyst, biaryl 11 was obtained in good yield *via* the Hiyama cross-coupling and dehydrochlorination (Fig. 4A, lower).¹⁴

A range of 1-aryl-1-fluoro-1,3-butadiens 10b–10d were successfully prepared from 8b–8d by C–Si bromination and following 1,3-butadiene formation (Fig. 4B). Desilylbromination of benzyl fluoride 8b prepared by C–F chlorination of difluoromethylene 7b and following dehydrochlorination furnished thiienyl-substituted 1-fluoro-1,3-butadiene 10b. Also, fluorobutadienes 10c and 10d were successfully synthesized from difluoromethylenes 7c and 7d having electron-deficient aromatic ring and transformable bromo group, respectively, in good yields. Since 1,3-butadienes are versatile building blocks in synthetic organic chemistry,¹⁵ this unique method to prepare functionalized fluorobutadienes will serve to synthesize a broad range of organofluorines.

In summary, we accomplished the synthesis of a wide variety of organofluorines through LAH reduction of *o*-(fluorosilyl)benzodifluorides. A broad range of benzyl fluorides and 1-aryl-1-fluoro-1,3-butadienes were successfully prepared by C–F transformations of *o*-(fluorosilyl)benzodifluorides and following transformations. Further studies such as diversifications of 1-aryl-1-fluoro-1,3-butadienes are ongoing in our laboratory.

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Conflicts of interest

There are no conflicts to declare.

Notes and references

- 1 (a) S. Purser, P. R. Moore, S. Swallow and V. Gouverneur, *Chem. Soc. Rev.*, 2008, **37**, 320; (b) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly and N. A. Meanwell, *J. Med. Chem.*, 2015, **58**, 8315.
- 2 T. Hiyama and H. Yamamoto, Organofluorine Building Blocks, in *Organofluorine Compounds*, ed. H. Yamamoto, Springer, Berlin, 2000, pp. 77–118.
- 3 (a) K. Fuchibe, R. Oki, H. Hatta and J. Ichikawa, *Chem. – Eur. J.*, 2018, **24**, 17932; (b) K. Komoda, R. Iwamoto, M. Kasumi and H. Amii, *Molecules*, 2018, **23**, 3292; (c) S. Kawamura, C. J. Henderson, Y. Aoki, D. Sekine, S. Kobayashi and M. Sodeoka, *Chem. Commun.*, 2018, **54**, 11276; (d) X. Zeng, W. Yan, S. B. Zacate, T.-H. Chao, X. Sun, Z. Cao, K. G. E. Bradford, M. Paeth, S. B. Tyndall, K. Yang, T.-C. Kuo, M.-J. Cheng and W. Liu, *J. Am. Chem. Soc.*, 2019, **141**, 11398; (e) N. Hisano, D. Kimura and K. Mori, *Chem. Lett.*, 2019, **48**, 771; (f) C. F. Meyer, S. M. Hell, A. Misale, A. A. Trabanco and V. Gouverneur, *Angew. Chem., Int. Ed.*, 2019, **58**, 8829; (g) L. Tang, Z.-Y. Liu, W. She and C. Feng, *Chem. Sci.*, 2019, **10**, 8701; (h) E. Miller, S. Kim, K. Gibson, J. S. Derrick and F. D. Toste, *J. Am. Chem. Soc.*, 2020, **142**, 8946; (i) X. Jiang, D. Meyer, D. Baran, M. A. C. González and K. J. Szabó, *J. Org. Chem.*, 2020, **85**, 8311; (j) L. Liao, R. An, H. Li, Y. Xu, J.-J. Wu and X. Zhao, *Angew. Chem., Int. Ed.*, 2020, **59**, 11010; (k) Q. Xie, Z. Zhu, L. Li, C. Ni and J. Hu, *Chem. Sci.*, 2020, **11**, 276; (l) M. Cloutier, M. Mamone and J.-F. Paquin, *Chem. Commun.*, 2020, **56**, 5969; (m) H. Kadri, T. E. Taher, Q. Xu, M. Sharif, E. Ashby, R. T. Bryan, B. E. Willcox and Y. Mehellou, *J. Med. Chem.*, 2020, **63**, 11258; (n) W. Wang, P. Wang, Q. Zhang, P. Du, J. Zhang, H. Deng and H. Jiang, *Tetrahedron*, 2020, **76**, 131477; (o) A. Tarui, M. Ueo, M. Morikawa, M. Tsuta, S. Iwasaki, N. Morishita, Y. Karuo, K. Sato, K. Kawai and M. Omote, *Synthesis*, 2020, 3657; (p) K. Kikushima, Y. Etou, R. Kamura, I. Takeda, H. Ito, M. Ohashi and S. Ogoshi, *Org. Lett.*, 2020, **22**, 8167; (q) H. Fang, Q. He, G. Liu and Z. Huang, *Org. Lett.*, 2020, **22**, 9298; (r) P. Wang, P. Du, Q. Sun, J. Zhang, H. Deng and H. Jiang, *Org. Biomol. Chem.*, 2021, **19**, 2023; (s) S.-Y. He, X.-W. Yan, H.-Y. Tu and X.-G. Zhang, *Org. Chem. Front.*, 2021, **8**, 4746.
- 4 (a) F. Jaroschik, *Chem. – Eur. J.*, 2018, **24**, 14572; (b) J.-D. Hamel and J.-F. Paquin, *Chem. Commun.*, 2018, **54**, 10224; (c) D. R. Carvalho and A. H. Christian, *Org. Biomol. Chem.*, 2021, **19**, 947; (d) G. Yan, K. Qiu and M. Guo, *Org. Chem. Front.*, 2021, **8**, 3915; (e) H.-J. Ai, X. Ma, Q. Song and X.-F. Wu, *Sci. China: Chem.*, 2021, **64**, 1630.
- 5 (a) H. Dang, A. M. Whittaker and G. Lalic, *Chem. Sci.*, 2016, **7**, 505; (b) I. Mallov, A. J. Ruddy, H. Zhu, S. Grimme and D. W. Stephan, *Chem. – Eur. J.*, 2017, **23**, 17692; (c) S. B. Munoz, C. Ni, Z. Zhang, F. Wang, N. Shao, T. Mathew, G. A. Olah and G. K. S. Prakash, *Eur. J. Org. Chem.*, 2017, 2322; (d) K. Chen, N. Berg, R. Gschwind and B. König, *J. Am. Chem. Soc.*, 2017, **139**, 18444; (e) H. Wang and N. T. Jui, *J. Am. Chem. Soc.*, 2018, **140**, 163; (f) D. B. Vogt, C. P. Seath, H. Wang and N. T. Jui, *J. Am. Chem. Soc.*, 2019, **141**, 13203; (g) C. Luo and J. S. Bandar, *J. Am. Chem. Soc.*, 2019, **141**, 14120; (h) D. Mandal, R. Gupta, A. K. Jaiswal and R. D. Young, *J. Am. Chem. Soc.*, 2020, **142**, 2572; (i) H. Iwamoto, H. Irimiya, M. Ohashi and S. Ogoshi, *J. Am. Chem. Soc.*, 2020, **142**, 19360; (j) M. Ikeda, T. Matsuzawa, T. Morita, T. Hosoya and S. Yoshida, *Chem. – Eur. J.*, 2020, **26**, 12333; (k) R. Gupta, D. Mandal, A. K. Jaiswal and R. D. Young, *Org. Lett.*, 2021, **23**, 1915; (l) N. Sugihara, K. Suzuki, Y. Nishimoto and M. Yasuda, *J. Am. Chem. Soc.*, 2021, **143**, 9308; (m) K. I. Burton, I. Elser, A. E. Waked, T. Wagener, R. J. Andrews, F. Glorius and D. W. Stephan, *Chem. – Eur. J.*, 2021, **27**, 11730; (n) Y.-C. Luo, F.-F. Tong, Y. Zhang, C.-Y. He and X. Zhang, *J. Am. Chem. Soc.*, 2021, **143**, 13971; (o) S. Mkrtchyan, M. Jakubczyk, S. Lanka, M. Yar, K. Ayub, M. Shkoor, M. Pittelkow and V. O. Iaroshenko, *Adv. Synth. Catal.*, 2021, **363**, 5448.
- 6 D. Mandal, R. Gupta and R. D. Young, *J. Am. Chem. Soc.*, 2018, **140**, 10682.
- 7 (a) S. Yoshida, K. Shimomori, Y. Kim and T. Hosoya, *Angew. Chem., Int. Ed.*, 2016, **55**, 10406; (b) Y. Kim, K. Kanemoto, K. Shimomori, T. Hosoya and S. Yoshida, *Chem. – Eur. J.*, 2020, **26**, 6136; (c) R. Idogawa, Y. Kim, K. Shimomori, T. Hosoya and S. Yoshida, *Org. Lett.*, 2020, **22**, 9292.
- 8 (a) V. H. T. Chang and J. Y. Corey, *J. Organomet. Chem.*, 1980, **190**, 217; (b) C. Eaborn and D. E. Reed, *J. Chem. Soc., Perkin Trans. 2*, 1985, 1687.
- 9 When the reaction was performed for 15 min, hydrosilane 7e was obtained in 24% yield along with 76% recovery of fluorosilane 5e.
- 10 (a) J. Ichikawa, S. Miyazaki, M. Fujiwara and T. Minami, *J. Org. Chem.*, 1995, **60**, 2320; (b) J.-P. Bégué, D. Bonnet-Delpont and B. Crousse, *Synlett*, 2004, 18; (c) T. Dohi, N. Yamaoka and Y. Kita, *Tetrahedron*, 2010, **66**, 5775.
- 11 B. Su and J. F. Hartwig, *J. Am. Chem. Soc.*, 2017, **139**, 12137.
- 12 T. J. O'Connor and F. D. Toste, *ACS Catal.*, 2018, **8**, 5947.
- 13 See the ESI‡ for details.
- 14 (a) Y. Hatanaka and T. Hiyama, *J. Org. Chem.*, 1989, **54**, 268; (b) H. F. Sore, W. R. J. D. Galloway and D. R. Spring, *Chem. Soc. Rev.*, 2012, **41**, 1845; (c) K. Hirabayashi, J. Kawashima, Y. Nishihara, A. Mori and T. Hiyama, *Org. Lett.*, 1999, **1**, 299.
- 15 For selected reviews on versatile transformations of 1,3-dienes, see: (a) J. Pyziak, J. Walkowiak and B. Marciniec, *Chem. – Eur. J.*, 2017, **23**, 3502; (b) Y. Xiong, Y. Sun and G. Zhang, *Tetrahedron Lett.*, 2018, **59**, 347; (c) X. Wu and L.-Z. Gong, *Synthesis*, 2019, 122.