

Chemical Science

rsc.li/chemical-science



ISSN 2041-6539

EDGE ARTICLE

Norio Shibata *et al.*

Cross-coupling of organic fluorides with allenes:
a silyl-radical-relay pathway for the construction of
 α -alkynyl-substituted all-carbon quaternary centres

Cite this: *Chem. Sci.*, 2024, 15, 5113

All publication charges for this article have been paid for by the Royal Society of Chemistry

Cross-coupling of organic fluorides with allenes: a silyl-radical-relay pathway for the construction of α -alkynyl-substituted all-carbon quaternary centres†

Jun Zhou,^a Zhengyu Zhao,^a Soichiro Mori,^b Katsuhiko Yamamoto^b and Norio Shibata^{*ab}

Controlling the transformation of versatile and reactive allenes is a considerable challenge. Herein, we report an efficient silylboronate-mediated cross-coupling reaction of organic fluorides with allenes to construct a series of sterically demanding α -ethynyl-containing all-carbon quaternary centers (ACQCs), using catalyst-free silyl-radical-relay reactions to selectively functionalize highly inert C–F bonds in organic fluorides. The key to the success of this transformation lies in the radical rearrangement of an *in situ*-generated allenyl radical to form a bulky tertiary propargyl radical; however, the transformation does not show efficiency when using the propargyl isomer directly. This unique reaction enables the cross-coupling of a tertiary carbon radical center with a C(sp²)–F bond or a benzylic C(sp³)–F bond. α -Ethynyl-containing ACQCs with (hetero)aromatic substituents and benzyl were efficiently synthesized in a single step using electronically and sterically diverse organic fluorides and allenes. The practical utility of this protocol is showcased by the late-stage functionalization of bioactive molecules and the modification of a liquid crystalline material.

Received 9th December 2023
Accepted 19th February 2024

DOI: 10.1039/d3sc06617g

rsc.li/chemical-science

Introduction

All-carbon quaternary centers (ACQCs) exhibit rigidity and structural diversity and are key structural units that occur frequently in many natural products, pharmaceuticals, and bioactive molecules.¹ Moreover, at least 12% of the 200 top-selling prescription drugs in the US since 2011 contain a stereo-quaternary carbon center.² Therefore, the construction of ACQCs presents a quite attractive challenge for organic synthetic chemists.³ In particular, ACQCs that contain an alkyne moiety serve as versatile intermediates and basic functionalized groups in organic transformations.⁴ Generally, the synthetic methods for alkyne-containing ACQCs involve either the direct introduction of alkynyl moieties into target molecules⁵ or the transformation from halogenated allenes in the presence of Knochel reagents.⁶ However, the aforementioned methodologies are associated with major drawbacks, including the use of transition-metal (TM) catalysts, dimerization of terminal alkynes, β -H elimination of branched tertiary alkyl units, and/or the reliance on special functionalized precursors. Therefore, the development of efficient strategies to overcome these limitations and the extremely

strong steric effect to realize alkynyl-substituted ACQCs through C–C bond coupling reactions remains challenging.

C–C bond formation is a perpetual subject of interest in organic chemistry and represents one of the most important transformations for the manufacture of products used in daily life.⁷ The majority of C–C bond coupling reactions require TM catalysts and/or organic (pseudo)halides (Ar/alkyl–X; X = *e.g.*, I, Br, Cl, OTf, OMs).⁸ However, organic fluorides are rarely employed as coupling partners because the C–F bond is rather inert and has a higher bond dissociation energy (BDE) (*e.g.*, fluorobenzene: 126 kcal mol^{−1}; 1-fluoropropane: 114 kcal mol^{−1}) compared with the corresponding C–I/Br/Cl bonds.⁹ Additionally, with the rapid development of synthetic methodologies,¹⁰ the abundance and ready accessibility of organofluorine compounds¹¹ make them attractive functional moieties as well as building blocks for further organic transformations.

Yet, the activation of robust C–F bonds remains a major challenge in contemporary chemistry. In this context, TM catalysis has proven a promising strategy for the direct functionalization of otherwise unreactive C–F bonds *via* the oxidative addition of C–F bonds to TMs followed by selective functionalization, providing access to the desired defluorinated molecules.¹² However, the selective activation of C–F bonds usually either suffers from high oxidative-addition barriers, thus the employment of highly elaborate TM catalysts¹³ and/or forcing conditions¹⁴ is often indispensable, or confined to

^aDepartment of Nanopharmaceutical Sciences, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan. E-mail: nozshiba@nitech.ac.jp

^bDepartment of Life Science and Applied Chemistry, Nagoya Institute of Technology, Gokiso, Showa-ku, Nagoya 466-8555, Japan

† Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d3sc06617g>



multi/poly-fluorinated arenes¹⁵ (Fig. 1A). Therefore, an alternative method that efficiently bypasses the high barriers required for the progress of the oxidative addition and that promotes the smooth coupling of C–F and C–H bonds under mild conditions would make a great contribution to this field.

Specifically, we envisioned that *in situ*-generated silyl radicals would quickly abstract a proton from targeted C–H reactants to form the corresponding C-centered radicals, thus enabling subsequent catalyst-free transformations with organic fluorides *via* the activation of an inert C–F bond to realize C–C coupling products (Fig. 1B). Such silyl-radical-relay reactions have already been demonstrated by our recently reported TM-free silylboronate ($R_3SiBpin$)-mediated cross-couplings of organic fluorides with alkenes/arylmethanes (Fig. 1C).¹⁶

Recently, the unique structural features and versatile reactivity of allenes enabled them to be not only a versatile functional group that is incorporated in natural products, pharmaceuticals, and organic materials,¹⁷ but also serve as an ideal platform for the development of new methodologies in synthetic transformations, chiral ligands or even catalysts.¹⁸ In this context, reactions between silylboronates and allenes have been pioneered by the Sugimoto group¹⁹ and further explored by Stratakis;²⁰ however, most hitherto reported protocols require TM catalysts and many provide silaboration products with one double bond retained. To date, only the Chen group²¹ has reported the successful transformation of vinylidene cyclopropanes into propargylic silanes in the presence of copper(I) chloride and NaO^tBu (Fig. 1D). Nevertheless, the silyl moiety is involved in the final products.

Based on these previous results, we designed a new silylboronate-mediated cross-coupling of organic fluorides with allenes to access ACQCs that feature an α -ethynyl group *via* C–F bond activation and radical rearrangement at room temperature (Fig. 1E).^{16,22} Initially, $R_3SiBpin$ and potassium *tert*-butoxide (KO^tBu) in an ether-based solvent smoothly generate intermediate **A**. Owing to the radical-initiation properties of KO^tBu ²³ and the steric demand of intermediate **A**, **A** splits into the bulky frustrated radical pair **B**,²⁴ which consists of a trialkylsilyl radical ($\cdot SiR_3$) and a boron-radical species (B^\cdot), *via* homolytic cleavage of the Si–B bond. The silyl radical in **B** then directly abstracts a hydrogen atom from the allene (**3**) to form allenyl radical-containing frustrated radical pair **C**, which could easily isomerize to the sterically highly demanding propargylic radical-containing frustrated radical pair **D**.²⁵ Subsequently, **D** would attract organic fluoride **1** or **2** by preferential interaction between the F atom and the **B** center to afford **TS-I**. Finally, the desired ethynyl-containing product with a quaternary carbon center (**4** or **5**) would be obtained *via* C–C bond coupling, accompanied by the release of **E** ($[Bpin(O^tBu)F]K$), which would promptly react with another equivalent of KO^tBu to provide a stable $[Bpin(O^tBu)_2]$ species and KF.

Results and discussion

Silylboronate-mediated cross-coupling reactions of aryl fluorides and aryl allenes

As depicted in our mechanistic hypothesis for the proposed C–C coupling (Fig. 1E), we expected that a silyl radical generated from the silylboronate and KO^tBu could abstract a hydrogen

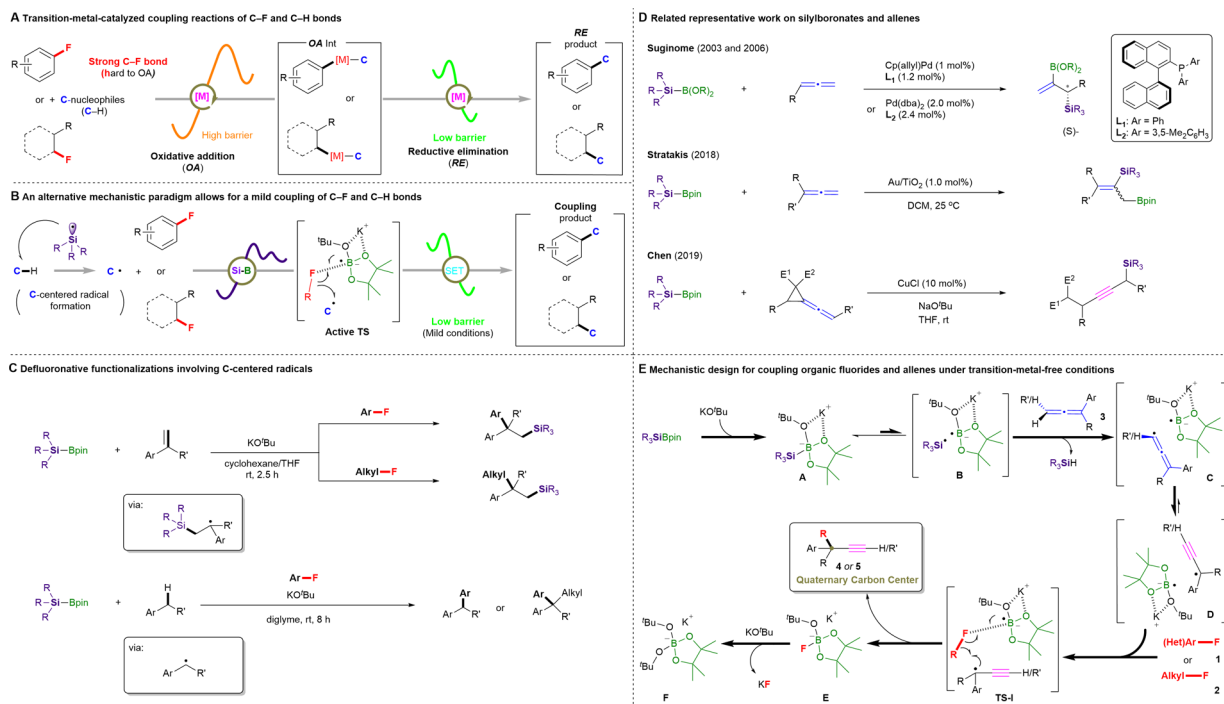


Fig. 1 Cross-couplings of C–F and C–H bonds. (A) Transition-metal-catalyzed coupling reactions of C–F and C–H bonds. (B) A low-barrier cross-coupling of C–F and C–H bonds enabled by silylboronate and KO^tBu . (C) Our previous defluorinative functionalization work involving C-centered radicals using silylboronates and organic fluorides. (D) Related representative work on silylboronates and allenes. (E) Mechanistic design for the cross-coupling of organic fluorides and allenes under transition-metal-free conditions (this work).



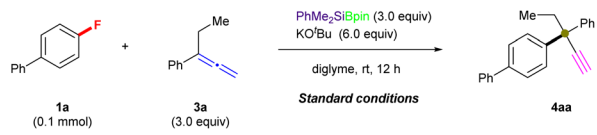
atom from the allene terminal. Therefore, we initiated the cross-coupling reactions by using 4-fluorobiphenyl (**1a**) and penta-1,2-dien-3-ylbenzene (**3a**) as model substrates. The desired product, 4-(3-phenylpent-1-yn-3-yl)biphenyl (**4aa**), which possesses a quaternary carbon center with an α -ethynyl moiety, was obtained in 34% yield under the standard reaction conditions [Et_3SiBpin (2.0 equiv.), KO^tBu (4.0 equiv.), THF, room temperature; entry 1, Table 1]. Furthermore, among the silylboronates tested under the same conditions, the Suginome reagent ($\text{PhMe}_2\text{SiBpin}$) improved the yield of **4aa** to 41% (entry 2). Subsequent optimization focused on screening the number of reactant equivalents, solvent, and reaction time in the presence of $\text{PhMe}_2\text{SiBpin}$ and finally afforded **4aa** in 94% yield under the optimized conditions (entry 3; for details, see the ESI; Tables S1–S4†). Control experiments showed that the reaction did not proceed in the absence of silylboronate or KO^tBu (entries 4). Moreover, the desired product was not obtained using other bases such as KOMe, NaO^tBu , LiO^tBu , or KHMDS (entries 5 and 6). This indicated that the counteranions in MO^tBu exhibited superior ability for K^+ over Na^+ or Li^+ in facilitating this transformation may lie in its established capacity to function as a single-electron reductant.²³ Decreasing the amount of $\text{PhMe}_2\text{SiBpin}$ or KO^tBu resulted in lower yields of **4aa** (86% and 51%, respectively; entries 7 and 8). Replacing $\text{PhMe}_2\text{SiBpin}$ with Et_3SiBpin under otherwise identical optimal conditions gave **4aa** in only 75% yield (71% isolated; entry 9). Additionally, the use of an inadequate amount of **3a** (2.0 equiv.) had a negative effect on the reaction yield (entry 10).

It should also be noted here that the Suginome reagent usually generates the undesired side product 1,2-di-*tert*-butoxy-1,1,2,2-tetramethyldisilane²⁶ (same polarity as **4aa**), which is formed by the dimerization of the *tert*-butoxydimethylsilyl radical ($^t\text{BuOMe}_2\text{Si}^\cdot$), which renders the purification of **4aa**

difficult *via* column chromatography on silica gel. Instead, the use of Et_3SiBpin afforded pure **4aa**, albeit in a lower yield. Furthermore, the slightly elevated reaction temperature (50 °C) could significantly reduce the consumption of both the Suginome reagent, KO^tBu , and allene **3a** to half the amount, with 79% yield (entry 11). However, only a 38% yield was observed when $\text{PhMe}_2\text{SiBpin}$ was replaced by Et_3SiBpin under the same conditions as in entry 11 (entry 12).

Scope and limitations. Then, the substrate scope of this silylboronate-mediated defluoronative cross-coupling was further evaluated using the optimal reaction conditions (entries 3 and 9, Table 1) in the presence of $\text{PhMe}_2\text{SiBpin}$ or Et_3SiBpin (Fig. 2). As shown in Fig. 2-I, (hetero)aryl fluorides with diverse electronic properties (**1**) were treated with **3a**. First, five types of fluorobenzenes with different substituents (**1a–1e**), including the sterically hindered *ortho*-substituted substrate **1c**, reacted efficiently with **3a** under the optimal conditions to generate the corresponding cross-coupling amination products (**4aa–4ea**) in high yield (48–87%). For example, biphenyl (**4aa**: 73%; **4ba**: 75%), *ortho*-OMe (**4ca**: 48%), and phenoxy (**4da**: 87%; **4ea**: 82%) products were all obtained using this methodology. Furthermore, a wide range of fluorobenzenes that contain π -extended moieties with various electronic properties were efficiently converted into the corresponding ethynyl-containing defluorinative products with an ACQC (**4fa–4la**) in good-to-high yield (52–90%), which is virtually independent of the attached functional group. The use of *p*-substituted fluorobenzenes with electron-donating (1-naphthyl–: **1f**; Me–: **1g**; MeO–: **1h**; BnO–: **1i**; benzo[1,3]dioxol–: **1j**) or electron-withdrawing groups (Cl–: **1k**; CF_3 : **1l**) successfully furnished the desired products (**4fa**: 76%; **4ga**: 63%; **4ha**: 89%; **4ia**: 84%; **4ja**: 90%; **4ka**: 52%; **4la**: 52%). The excellent chemoselectivity profile of this coupling reaction is nicely illustrated by the tolerance of the reaction conditions

Table 1 Optimization of the cross-coupling conditions^a



Entry	Variation from the “standard conditions”	4aa ^b (%)
1	Et_3SiBpin (2.0 equiv.), KO^tBu (4.0 equiv.), THF	34
2	$\text{PhMe}_2\text{SiBpin}$ (2.0 equiv.), KO^tBu (4.0 equiv.), THF	41
3	None	94
4	Without $\text{PhMe}_2\text{SiBpin}$ or KO^tBu	0
5	KOMe instead of KO^tBu	0
6	NaO^tBu , LiO^tBu or KHMDS instead of KO^tBu	Trace
7	$\text{PhMe}_2\text{SiBpin}$ (2.5 equiv.) and KO^tBu (5.5 equiv.) instead	86
8	$\text{PhMe}_2\text{SiBpin}$ (2.0 equiv.) and KO^tBu (4.0 equiv.) instead	51
9 ^c	Et_3SiBpin instead of $\text{PhMe}_2\text{SiBpin}$	75(71)
10	3a (2.0 equiv.) instead	78
11	$\text{PhMe}_2\text{SiBpin}$ (1.5 equiv.) and KO^tBu (3.0 equiv.) and 3a (1.5 equiv.) at 50 °C	79
12	Et_3SiBpin (1.5 equiv.) and KO^tBu (3.0 equiv.) and 3a (1.5 equiv.) at 50 °C	38

^a Unless otherwise noted, the standard reactions refer to: **1a** (17.2 mg, 0.1 mmol), **3a** (43.2 mg, 0.3 mmol), $\text{PhMe}_2\text{SiBpin}$ (78.7 mg, 0.3 mmol), KO^tBu (67.2 mg, 0.6 mmol), and diglyme (1.0 mL); room temperature; 12 h. ^b Determined by ^{19}F NMR and ^1H NMR spectroscopy using 3-fluoropyridine as the internal standard. ^c The isolated yield is shown in parentheses.



stability of the generated radical, which is indispensable for a successful transformation.

After evaluating the ranges of **1** and **3** in this coupling reaction, we then further demonstrated the scope of this feasible coupling reaction using various combinations of **1** and **3** (Fig. 2-III). Fluoroarenes with phenyl (**1b**), electron-donating (**1d**, **1e**, **1g**, and **1h**), and electron-withdrawing (**1k** and **1l**) substituents were coupled with various allenes to generate the desired α -ethynyl-substituted quaternary center products **4** in good yields (**4bg**: 86%; **4dg**: 89%; **4di**: 91%; **4ek**: 86%; **4gc**: 60%; **4hg**: 94%; **4hh**: 77%; **4kh**: 73%; **4lg**: 62%), and even the complete transformation of **1l** into **4lg** was achieved within 2 hours with the potentially cleavable C–F bonds of the trifluoromethyl group remaining intact. The reactions of *N*-heterocycle-containing aryl fluorides (**1n**, **1o**, **1q**, and **1r**) with substituted-allenes (**3c**, **3g**, **3i**, and **3k**) under standard conditions mediated by PhMe₂SiBpin resulted in pyridine derivatives and 1*H*-pyrrole derivatives in good-to-high yields (**4nc**: 74%; **4oi**: 67%; **4qg**: 79%; **4rk**: 87%). Additionally, 2-fluorobenzofuran (**1u**) is also an acceptable coupling partner, giving **4ui** in a moderate yield of 51%.

Furthermore, we repeated the defluorinative cross-coupling reactions under the heating reaction conditions (entry 11, Table 1) by using representative aryl fluorides **1** with allene **3a** (Fig. 3). First, as shown in Fig. 3-I, four types of π -extended aryl fluorides substituted with electron-donating (**1a**, **1h** and **1j**) and withdrawing (**1k**) groups were evaluated, and the desired α -ethynyl-containing ACQCs were observed in ¹H NMR yields of \leq 82% (**4aa**: 79%; **4ha**: 75%; **4ja**: 82%; **4ka**: 73%) and with 77% isolated yield for **4ja**. Notably, *N*-containing heteroaromatic fluorides (**1n–1t**) were successfully coupled with **3a** under the same conditions (entry 11, Table 1) to afford the corresponding coupling products with an ACQC in moderate to high ¹H NMR yields (**4na**: 62%; **4oa**: 32%; **4qa**: 46%; **4ra**: 89%), whereas desired product **4ta** could be obtained in 68% isolate yield by

coupling active 2-fluoro-5-phenylpyridine (**1t**) and allene **3a**. Similarly, 2-fluorobenzofuran (**1u**) and the simplest polycyclic aromatic fluoride (**1v**) were efficiently coupled with allene **3a** to afford **4ua** and **4va** in 66% and 59% yield, respectively. Additionally, fluorobenzene substituted with triethylsilyl (**1w**), trifluoromethyl (**1x**), bromo (**1y**), methyl (**1z**), methoxyl (**1aa**), and *N,N*-dimethyl (**1ab**) were also coupled with allene **3a**, albeit in low yields (**4wa**: 40% isolated yield; **4xa**: 41% isolated yield; **4ya**: 12%; **4za**: 23%; **4aaa**: 13%; **4aba**: 0%). Thus, the lower yield regarding the substituted fluorobenzenes (especially for **1z**, **1aa**, and **1ab**) could be explained by their C(sp²)–F bond possessing higher BDE than that of substituted biaryl fluorides. In this case, a complex mixture (containing **12** or **15**) was obtained rather than the desired products with an ACQC. However, carbonyl containing fluorobenzenes, such as carboxylate (**1ac**), resulted in no desired product under the aforementioned conditions with or without heating (Fig. 3-I).

To our delight, the cross-coupling of benzyl fluorides **2** with allene **3a** under similar reaction conditions while at room temperature were also successful in affording desired products with ACQCs (Fig. 3-II). Primary benzyl fluorides bearing electron-donating substituents (phenyl: **2a**; *tert*-butyl: **2e**) and electron-withdrawing substituents (trifluoromethoxy: **2b**; chloro: **2c**; bromo: **2d**) reacted efficiently with allene to afford the corresponding products in up to 89% yield (**5aa**: 89%; **5ba**: 65%; **5ca**: 83%; **5da**: 59%; **5ea**: 86%). Additionally, the naphthyl-containing primary fluorides (**2f** and **2g**) successfully yielded the desired products (**5fa**: 80%; **5ga**: 73%) in good yields regardless of the α / β -substituted position on the naphthalene ring. However, secondary alkyl fluorides **2h** furnished the desired coupling product **5ha** in <10% ¹H NMR yield, even when the reaction was performed at 50 °C. Additionally, the primary aliphatic alkyl fluorides (**2i** and **2j**) did not afford the corresponding products even under heating.

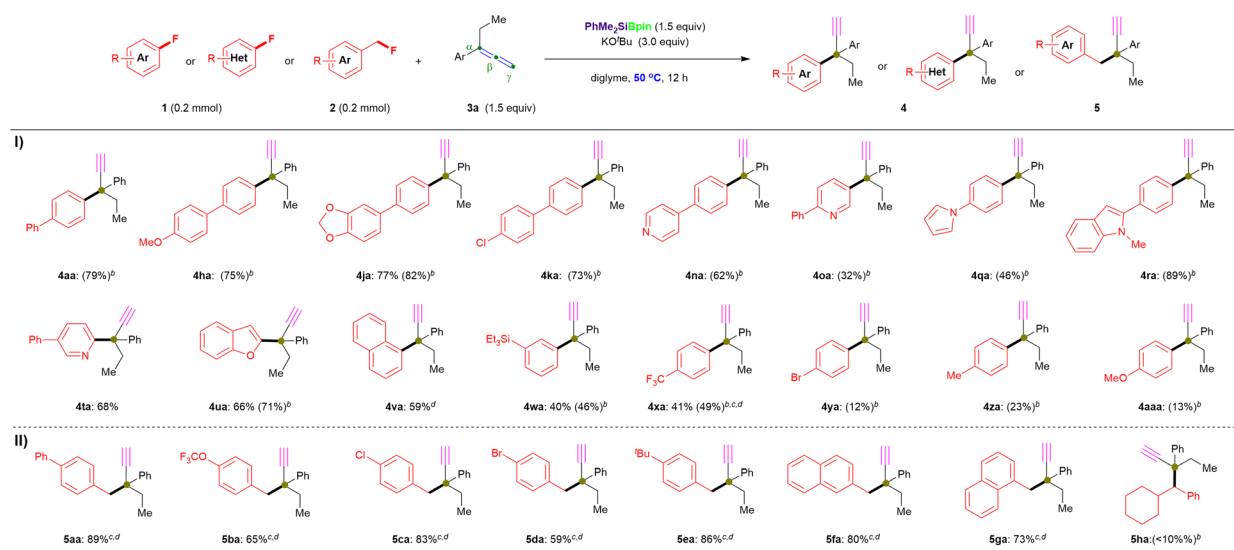


Fig. 3 Further scopes and limitations. ^a Unless otherwise noted, all reactions were conducted using **1** or **2** (0.2 mmol), **3a** (43.2 mg, 1.5 equiv.), PhMe₂SiBpin (78.7 mg, 1.5 equiv.), KO^tBu (67.5 mg, 3.0 equiv.), and diglyme (1.5 mL) at 50 °C for 12 h. ^b The ¹H NMR yields are shown in the parentheses. ^c Reactions were performed at room temperature. ^d Reactions were performed using Et₃SiBpin.



Synthetic applications. To highlight the synthetic applications of this silylboronate-mediated defluorinative coupling reaction, some easily accessible functional molecules with α -alkynylated quaternary centers were obtained after several drug derivatives and liquid-crystalline materials were evaluated under the standard conditions (Fig. 4A). Adapalene derivative **4adc** with two substituents at the β -position was successfully obtained in 71% yield by coupling β -fluoronaphthyl-containing adapalene derivative **1ad** with allene **3c**. Steroid derivative **4aei** was synthesized in 42% yield *via* the defluorinative coupling of fluoro-incorporated estrone derivative **1ae** and **3i**. Blonanserin derivative **4afg** underwent the coupling reaction with **3g** to generate Blonanserin derivative **4afg** in 89% yield. Moreover, the liquid-crystalline material **1ag** was successfully functionalized using this transformation with **3g** to give **4agg** in 67% yield. The presence of the α -ethynyl group in these derivatives could potentially allow further late-stage functionalization.

Synthetic transformations. It is noteworthy that quenching with different reagents efficiently afforded a variety of products with functional moieties. Specifically, the cross-coupling of **1a** with **3a** under the standard conditions afforded **6** (62% yield) and *d*-**4aa** (70% yield) when quenched using *p*-anisaldehyde and deuterium oxide, respectively. Bromoethynyl derivative **7** (89% yield) was also successfully synthesized when the coupling reaction of **1a** with **3g** was quenched with *N*-bromosuccinimide (NBS) in the presence of a catalytic amount of silver(i) nitrate (Fig. 4B, left). Additionally, **4aa** can serve as a versatile precursor for further synthetic transformations. First, a gram-scale

reaction of **1a** and **3a** proceeded smoothly to afford **4aa** in 68% yield under the standard conditions in the presence of Et_3SiBpin . Thereafter, a dual catalyst ($\text{Pd}(\text{OAc})_2/\text{PPh}_3$ and CuI) enabled the cross-coupling reaction of **4aa** with a substituted aryl bromide,²⁷ which furnished the phenyl-coupling product **8** (95% yield) in the presence of Et_3N in THF at 80 °C. Treatment of **4aa** with trimethylsilyl chloride (TMS-Cl) in the presence of butyllithium furnished TMS-acetylene product **9** (95% yield).²⁸ A Pd/C-catalyzed reduction of **4aa** employing acetic acid/ NaBH_4 afforded hydrocarbon product **10** in 88% yield (Fig. 4B, right).²⁹ These straightforward functionalization reactions significantly expand the scope and utility of these silyl-radical-relay cross-coupling reactions between aryl fluorides and allenes.

Mechanistic study. To shed further light on the postulated coupling mechanism of aryl fluorides and allenes envisioned in Fig. 1E, several control experiments were conducted (Fig. 5). The uniqueness of this silylboronate-mediated cross-coupling reaction using aryl fluorides **1**, rather than conventional aryl (pseudo)halides Ar-X **11a-d** ($\text{X} = \text{Cl}, \text{Br}, \text{I}, \text{or OTf}$), was revealed *via* parallel experiments (Fig. 5A). 4-Chlorobiphenyl (**11a**) was converted to the desired coupling product **4aa** in 28% yield under the same conditions (Table 1, entry 3). However, the use of bromo-, iodo-, or TfO-substituted biphenyl (Br: **11b**; I: **11c**; TfO: **11c**) generated a complex mixture, in which the desired cross-coupling product **4aa** was barely detected. Instead, the by-product 1,2-di-*tert*-butoxy-1,1,2,2-tetramethyldisilane largely accumulated (determined by ^1H NMR; for details, see the ESI[†]) (Fig. 5A). We then attempted the reaction using the ethynyl

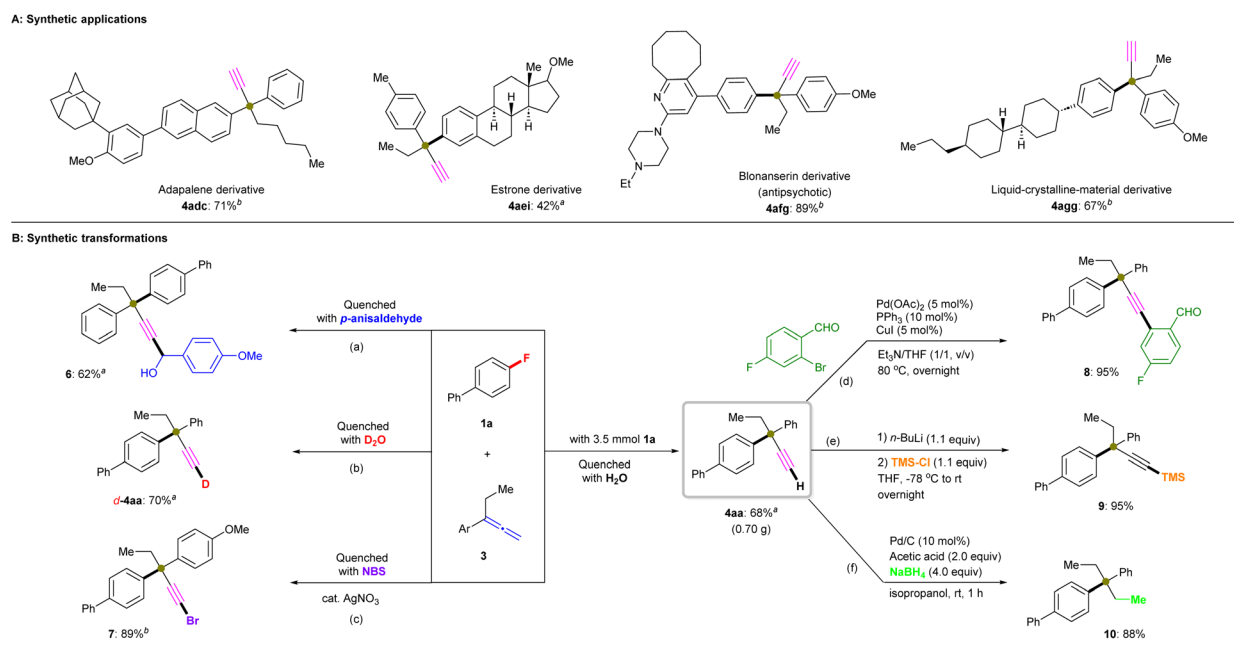


Fig. 4 Synthetic utility. (A) Synthetic applications. Unless otherwise noted, all reactions were conducted using **1** (0.2 mmol), **3** (3.0 equiv.), R_3SiBpin (3.0 equiv.), KO^tBu (135 mg, 6.0 equiv.), and diglyme (2.0 mL) at room temperature for 12 h (isolated yields are shown). (B) Synthetic transformations. ^a Reaction performed using Et_3SiBpin . ^b Reaction performed using $\text{PhMe}_2\text{SiBpin}$. (a) **1a** (0.2 mmol), **3a** (0.6 mmol), *p*-anisaldehyde (0.3 mmol); (b) **1a** (0.2 mmol), **3a** (0.6 mmol), D_2O (2.0 mL); (c) **1a** (0.2 mmol), **3g** (0.6 mmol), NBS (0.4 mmol), AgNO_3 (0.1 mmol); (d) **4aa** (0.2 mmol), $\text{Pd}(\text{OAc})_2$ (0.01 mmol), PPh_3 (0.02 mmol), CuI (0.01 mmol), aryl bromide (0.24 mmol), $\text{Et}_3\text{N}/\text{THF}$ (1.0 mL, 1/1, v/v), 80 °C, overnight; (e) **4aa** (0.2 mmol), *n*-BuLi (0.24 mmol), TMS-Cl (0.22 mmol), THF (1.0 mL), -78 °C to rt, overnight; (f) **4aa** (0.2 mmol), Pd/C (0.02 mmol), acetic acid (0.04 mmol), NaBH_4 (0.8 mmol), rt, 1 h.



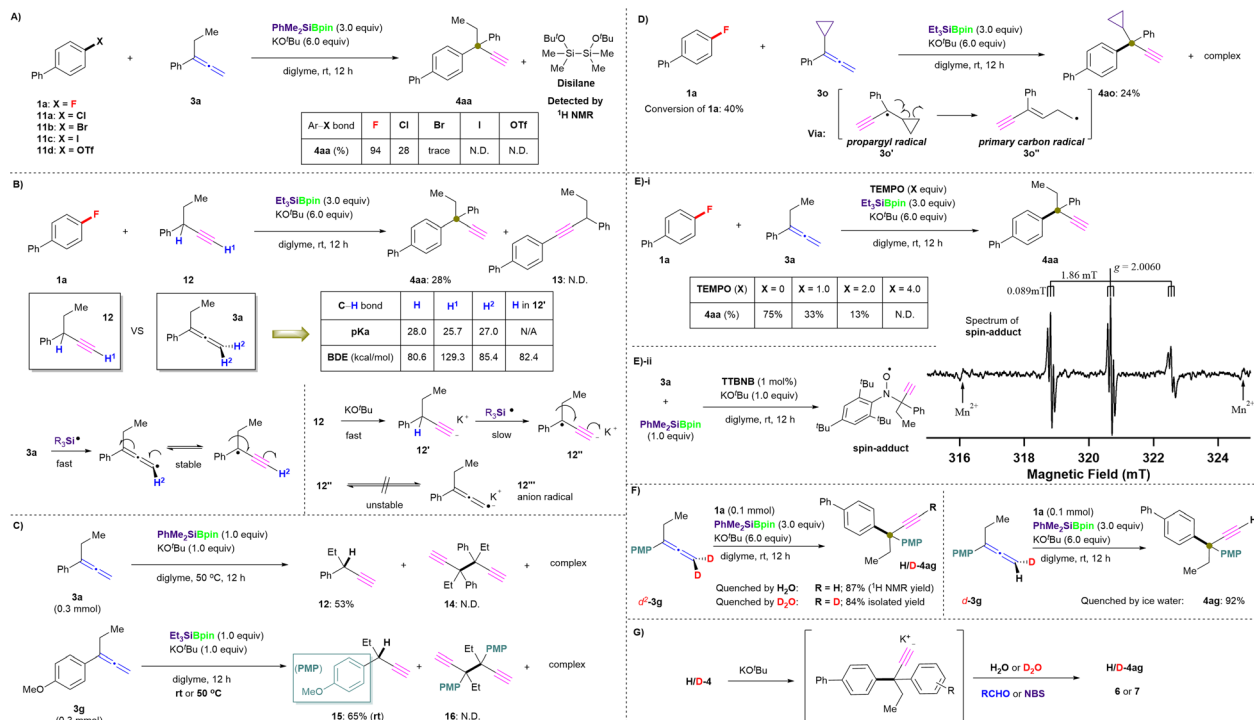


Fig. 5 Mechanistic study. (A) Chemoselectivities of organic (pseudo)halides Ar-X. (B) An attempt to use an alternative process. (C) Homocoupling attempt of generated propargyl radicals. (D) Radical ring-opening reaction. (E) Effect of TEMPO on this silylboronate-mediated coupling reaction (i) and ESR experiment in the presence of spin trapping reagent TTBNB (ii). (F) Kinetic-isotope-effect experiments. (G) Possible mechanism for the quenching process.

isomer of **3a**, *i.e.*, 3-phenyl-1-pentyne (**12**). While **3a** and **12** are isomers of each other, their pK_a values differ significantly, and **12** should be more reactive under the basic conditions (pK_a of **12**: H = 28.0; H¹ = 25.7; pK_a of **3a**: H² = 27.0).³⁰ Interestingly, the use of **1a** and **12** under the standard conditions (for details, see the ESI†) only afforded **4aa** in 28% ^1H NMR yield, and alkynyl adduct **13** was not detected; instead, the corresponding defluorosilylation product, *i.e.*, 4-biphenyltriethylsilane (4-Ph-C₆H₄-SiEt₃) was detected (Fig. 5B). This result excludes both the anionic *pre*-allenyl/propargyl-isomerization pathway from **3a** to **12** and the anionic $\text{S}_\text{N}\text{Ar}$ pathway. In contrast, the predicted bond dissociation energy (BDE)⁹ of C-H² in **3a** (85.4 kcal mol⁻¹) was higher than that of C-H (80.6 kcal mol⁻¹) but much smaller than that of C-H¹ in **12** (129.3 kcal mol⁻¹). Thus, radical cleavage of C-H² in **3a** is preferable to that of C-H¹ in **12**, and the low yield of **4aa** can be explained by the tertiary propargyl C-H bond in **12** which could be radically removed owing to its low BDE value; however, owing to the high acidity of C-H¹ in **12**, C-H¹ is promptly deprotonated by KO^tBu to provide potassium acetylide **12'** (BDE of C-H in **12'**: 82.4 kcal mol⁻¹). Thus, the generation of tertiary propargylic radicals is slow because of the instability of the generated radical anion isomers. When allene **3a** was treated with the Suginome reagent and KO^tBu at 50 °C in diglyme, only **12** was obtained (53% isolated yield). However, self-coupling dimer product **14** was not observed, which might be due to high steric repulsion. Similarly, allene **3g** gave the same result using Et_3SiBpin regardless of whether it reacted at room temperature or 50 °C, that is, **15** (65% isolated yield)

without the observation of **16** (Fig. 5C). In addition, a radical-clock experiment employing **1a** and α -cyclopropyl substituted allene (**3o**) was conducted. The conversion of **1a** was only 40% (determined by ^{19}F NMR; for details, see the ESI†), whereas **3o** was fully consumed to give a complex mixture (Fig. 5D). Fortunately, the desired product (**4ao**) was isolated in 24% yield, which agrees with our ^1H NMR analysis of the crude reaction mixture (for details, see the ESI†). The low yield of **4ao** can be explained by the low reactivity of the primary carbon radical **3o''** generated *via* the ring-opening process. We then evaluated the effect of (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) on the coupling reaction between **1a** and **3a** under the optimal conditions in the presence of Et_3SiBpin . Although **4aa** was obtained in a yield of 75% (^1H NMR yield) under standard conditions, the yield decreased significantly when the amount of TEMPO was increased (1.0 equiv. of TEMPO: 33%; 2.0 equiv. of TEMPO: 13%; 4.0 equiv. of TEMPO: 0%; Fig. 5E-i). It should be noted that the premixed silylboronate and KO^tBu were used to prevent TEMPO from being consumed by the reducing reagent silylboronate, followed by the addition of TEMPO and other materials. No desired product **4aa** was detected, which indicated that the *in situ* generated silyl radical should be fully trapped by TEMPO (for details, see the ESI†). ESR experiments were also performed. Since we have already demonstrated the generation of silyl radicals from Et_3SiBpin and KO^tBu under the same reaction conditions,^{16b} we tried to find the radical species derived from allene **3**. As expected, the ESR spectrum (triplet-triplet) was detected for the reaction of $\text{PhMe}_2\text{SiBpin}$, KO^tBu ,



and allene **3a** in diglyme at room temperature, which was assigned to the spin-adduct of the *tert*-propargyl radical trapped by 2,4,6-tri-*tert*-butylnitrosobenzene (TTBNB) (Fig. 5E-ii).³¹ Namely, the hyperfine splitting (hfs) constant due to nitrogen (A_N ; spin quantum number $I = 1$) was 1.86 mT, and the small splitting constant due to the two hydrogens at the *meta*-position of the TTBNB benzene ring (A_{Hm} ; $I = 1/2$) was 0.089 mT. The g -value of 2.006 was assigned to a nitroxide-type radical. Although further studies are required to show clear evidence, this observation strongly supports the formation of the propargyl radical (see the ESI† for details).

The kinetic-isotope effect of the C–H/C–D cleavage under ionic conditions is more substantially observed than that by the radical reactions.³² Thus, we evaluated **1a** in combination with deuterated allenes (d^2 -**3g** and d -**3g**) in several parallel reactions under the standard conditions in the presence of PhMe₂SiBpin (Fig. 5F). However, independent of the existence of deuterium in allene **3g**, the formation of D- or H-**4ag** depends on the quenching method, *i.e.*, on using H₂O or D₂O, even when quenching with ice water. The formed products **4/5** should exist as potassium acetylides in the reaction mixture, as the excess of ^tBuOK could easily result in a further deprotonation process. Therefore, the acetylide can be captured by D⁺, H⁺, Br⁺, RCHO, *etc.* (Fig. 5G). Besides, due to the high acidity of the C(sp)–H/D moiety in the terminal alkynyl position of **4ag**, the H/D exchange occurs easily during the workup steps.^{32,33} Interestingly, the reaction time and yield were almost identical independent of the use of **3g**, d^2 -**3g**, or d -**3g**. Therefore, we concluded that the C(sp²)–H/D bond cleavage should occur prior to the C–F bond cleavage, and thus the C(sp²)–H/D bond cleavage should not be the rate-limiting step. All observations in the mechanistic study led us to conclude that this defluorinative cross-coupling reaction proceeds *via* a single-electron transfer (SET)/radical process, in accordance with our mechanistic hypothesis shown in Fig. 1E.

Conclusions

In summary, we have realized the first cross-coupling reaction of organic fluorides with allenes to construct a library of α -ethynyl-containing all-carbon quaternary centers *via* C–F bond and C(sp²)–H bond radical cross-couplings using a silyl-radical-relay strategy. The C–F bond cleavage occurs concomitant with the formation of an isomerized propargylic radical, which takes place through cleavage of a C(sp²)–H bond, to cooperatively form a new C–C(sp³) bond. A notable feature of this cross-coupling reaction is that the *in situ*-generated silyl radical is able to directly abstract a proton from a C(sp²)–H bond of the allene to form an allenyl radical, which then easily isomerizes to form a propargylic radical that exerts a more profound steric influence. Significantly, in this transformation it is not possible to use the corresponding propargyl isomers directly instead of the allenes. This method proceeds under very mild conditions and efficiently obviates the use of TM catalysis or light irradiation to allow a range of *para*-, *meta*-, and even *ortho*-substituted (hetero)aryl fluoride, benzyl fluoride and allene substrates to undergo the normally challenging defluorinative coupling

process to afford all-carbon quaternary centers in moderate-to-excellent yield, with good functional-group compatibility and C–F bond selectivity. This radical-coupling system was further extended to the late-stage functionalization of several biologically active molecules.

Data availability

The data that support the findings of this study are available within the article and the ESI.† Details about materials and methods, experimental procedures, characterization data, mechanistic studies, ESR study and NMR spectral are included. All relevant data are also available from the authors.

Author contributions

JZ optimized the reaction conditions. JZ and ZZ surveyed the substrate scope, analyzed the data, and then discussed the results with NS. JZ, ZZ, and SM prepared the starting materials. ZZ and KY performed the ESR experiment and analyzed the data. JZ and NS wrote the manuscript. NS supervised the project. All authors contributed to the manuscript and have approved the final version of the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The present study was supported by the Japan Science and Technology Agency's (JST) CREST program entitled "Precise Material Science for Degradation and Stability" (JPMJCR21L1) Japan.

Notes and references

- (a) C. J. Douglas and L. E. Overman, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5363–5367; (b) K. W. Quasdorf and L. E. Overman, *Nature*, 2014, **516**, 181–191; (c) Y. Liu, S. J. Han, W. B. Liu and B. M. Stoltz, *Acc. Chem. Res.*, 2015, **48**, 740–751; (d) X. P. Zeng, Z. Y. Cao, Y. H. Wang, F. Zhou and J. Zhou, *Chem. Rev.*, 2016, **116**, 7330–7396; (e) T. Ling and F. Rivas, *Tetrahedron*, 2016, **72**, 6729–6777; (f) W. Chen and H. Zhang, *Sci. China: Chem.*, 2016, **59**, 1065–1078; (g) C. Li, S. S. Ragab, G. Liu and W. Tang, *Nat. Prod. Rep.*, 2020, **37**, 276–292; (h) Z. Xin, H. Wang, H. He and S. Gao, *Tetrahedron Lett.*, 2021, **71**, 153029; (i) W. Xue, X. Jia, X. Wang, X. Tao, Z. Yin and H. Gong, *Chem. Soc. Rev.*, 2021, **50**, 4162–4184.
- (a) M. Bartholow, *Pharmatimes*, 2012, **78**, 48–51; (b) Z. X. Wang and B. J. Li, *J. Am. Chem. Soc.*, 2019, **141**, 9312–9320.
- (a) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756; (b) B. Wang and Y. Q. Tu, *Acc. Chem. Res.*, 2011, **44**, 1207–1222; (c) L. Süssé and B. M. Stoltz, *Chem. Rev.*, 2021, **121**, 4084–4099.



- 4 (a) X. Huang, S. Wu, W. Wu, P. Li, C. Fu and S. Ma, *Nat. Commun.*, 2016, **7**, 12382; (b) S. L. Zhang, W. W. Zhang and B. J. Li, *J. Am. Chem. Soc.*, 2021, **143**, 9639–9647; (c) T. B. Poulsen, L. Bernardi, J. Alemán, J. Overgaard and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2007, **129**, 441–449; (d) M. B. Haughey, K. E. Christensen, D. L. Poole and T. J. Donohoe, *Chem. Sci.*, 2021, **12**, 13392–13397; (e) J. A. Dabrowski, F. Gao and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2011, **133**, 4778–4781; (f) Q. Q. Zhang, S. Y. Chen, E. Lin, H. Wang and Q. Li, *Org. Lett.*, 2019, **21**, 3123–3126.
- 5 (a) C. H. Ding and X. L. Hou, *Chem. Rev.*, 2011, **111**, 1914–1937; (b) W. Liu, L. Li and C. J. Li, *Nat. Commun.*, 2015, **6**, 6526–6531; (c) K. Tsuchida, Y. Senda, K. Nakajima and Y. Nishibayashi, *Angew. Chem., Int. Ed.*, 2016, **55**, 9728–9732; (d) B. V. M. Teodoro and L. F. Silva, *J. Org. Chem.*, 2017, **82**, 11787–11791; (e) Y. Xia, S. Feng, Z. Liu, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2015, **54**, 7891–7894; (f) M. Q. Tian, Z. Y. Shen, X. Zhao, P. J. Walsh and X. H. Hu, *Angew. Chem., Int. Ed.*, 2021, **60**, 9706–9711.
- 6 (a) A. M. Caporusso, S. Filippi, F. Barontini and P. Salvadori, *Tetrahedron Lett.*, 2000, **41**, 1227–1230; (b) A. M. Caporusso, A. Zampieri, L. A. Aronica and D. Banti, *J. Org. Chem.*, 2006, **71**, 1902–1910.
- 7 (a) E. J. Corey and X. M. Cheng, *The Logic of Chemical Synthesis*, Wiley, New York, 1989; (b) H. Mayr, B. Kempf and A. R. Ofial, *Acc. Chem. Res.*, 2003, **36**, 66–77; (c) N. G. Schmidt, E. Eger and W. Kroutil, *ACS Catal.*, 2016, **6**, 4286–4311; (d) D. Ravelli, S. Protti and M. Fagnoni, *Chem. Rev.*, 2016, **116**, 9850–9913; (e) G. Brahmachari, *RSC Adv.*, 2016, **6**, 64676–64725.
- 8 (a) J. Tsuji, *Transition Metal Reagents and Catalysts: Innovations in Organic Synthesis*, Wiley, Chichester, UK, 2000; (b) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.*, 2010, **110**, 624–655; (c) X. Chen, K. M. Engle, D. H. Wang and J. Q. Yu, *Angew. Chem., Int. Ed.*, 2009, **48**, 5094–5115; (d) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740–4761; (e) C. S. Yeung and V. M. Dong, *Chem. Rev.*, 2011, **111**, 1215–1292.
- 9 Y. R. Luo, *Comprehensive Handbook of Chemical Bond Energies*, CRC Press, Boca Raton, 2007.
- 10 (a) J. A. Ma and D. Cahard, *Chem. Rev.*, 2004, **104**, 6119–6146; (b) T. Furuya, A. S. Kamlet and T. Ritter, *Nature*, 2011, **473**, 470–477; (c) M. G. Campbell and T. Ritter, *Chem. Rev.*, 2015, **115**, 612–633; (d) S. Preshlock, M. Tredwell and V. Gouverneur, *Chem. Rev.*, 2016, **116**, 719–766; (e) Y. Zhu, J. Han, J. Wang, N. Shibata, M. Sodeoka, V. A. Soloshonok, J. A. S. Coelho and F. D. Toste, *Chem. Rev.*, 2018, **118**, 3887–3964; (f) S. D. Schimmler, M. A. Cismesia, P. S. Hanley, R. D. J. Froese, M. J. Jansma, D. C. Bland and M. S. Sanford, *J. Am. Chem. Soc.*, 2017, **139**, 1452–1455; (g) B. Xing, C. Ni and J. Hu, *Angew. Chem., Int. Ed.*, 2018, **57**, 9896–9900.
- 11 (a) Y. Ogawa, E. Tokunaga, O. Kobayashi, K. Hirai and N. Shibata, *iScience*, 2020, **23**, 101467; (b) M. Inoue, Y. Sumii and N. Shibata, *ACS Omega*, 2020, **5**, 10633–10640.
- 12 (a) J. L. Kiplinger, T. G. Richmond and C. E. Osterberg, *Chem. Rev.*, 1994, **94**, 373–431; (b) H. Amii and K. Uneyama, *Chem. Rev.*, 2009, **109**, 2119–2183; (c) T. Ahrens, J. Kohlmann, M. Ahrens and T. Braun, *Chem. Rev.*, 2015, **115**, 931–972; (d) L. Fu, Q. Chen and Y. Nishihara, *Chem. Rec.*, 2021, **21**, 3394–3410; (e) B. Zhao, T. Rogge, L. Ackermann and Z. Shi, *Chem. Soc. Rev.*, 2021, **50**, 8903–8953; (f) R. Ma, H. Hu, X. Li, G. Mao, Y. Song and S. Xin, *Catalysis*, 2022, **12**, 1665.
- 13 (a) V. P. W. Böhm, C. W. K. Gstöttmayr, T. Weskamp and W. A. Herrmann, *Angew. Chem., Int. Ed.*, 2001, **40**, 3387–3389; (b) P. Tian, C. Feng and T. P. Loh, *Nat. Commun.*, 2015, **6**, 7472–7478; (c) D. Zell, U. Dhawa, V. Müller, M. Bursch, S. Grimme and L. Ackermann, *ACS Catal.*, 2017, **7**, 4209–4213.
- 14 (a) M. Tobisu, T. Xu, T. Shimasaki and N. Chatani, *J. Am. Chem. Soc.*, 2011, **133**, 19505–19511; (b) D. Yu, L. Lu and Q. Shen, *Org. Lett.*, 2013, **15**, 940–943; (c) J. Li, C. Wu, B. Zhou and P. J. Walsh, *J. Org. Chem.*, 2018, **83**, 2993–2999; (d) Y. Yin, X. Yue, Q. Zhong, H. Jiang, R. Bai, Y. Lan and H. Zhang, *Adv. Synth. Catal.*, 2018, **360**, 1639–1643; (e) J. He, K. Yang, J. Zhao and S. Cao, *Org. Lett.*, 2019, **21**, 9714–9718.
- 15 (a) T. Schaub, P. Fischer, A. Steffen, T. Braun, U. Radius and A. Mix, *J. Am. Chem. Soc.*, 2008, **130**, 9304–9317; (b) S. Senaweera and J. D. Weaver, *J. Am. Chem. Soc.*, 2016, **138**, 2520–2523; (c) Z. J. Luo, H. Y. Zhao and X. Zhang, *Org. Lett.*, 2018, **20**, 2543–2546.
- 16 (a) J. Zhou, B. Jiang, Y. Fujihira, Z. Zhao, T. Imai and N. Shibata, *Nat. Commun.*, 2021, **12**, 3749–3757; (b) J. Zhou, Z. Zhao, B. Jiang, K. Yamamoto, Y. Sumii and N. Shibata, *Chem. Sci.*, 2023, **14**, 4248–4256.
- 17 (a) A. Hoffmann-Röder and N. Krause, *Angew. Chem., Int. Ed.*, 2004, **43**, 1196–1216; (b) S. Song, J. Zhou, C. Fu and S. Ma, *Nat. Commun.*, 2019, **10**, 507–515; (c) C. Y. He, Y. X. Tan, X. Wang, R. Ding, Y. F. Wang, F. Wang, D. Gao, P. Tian and G. Q. Lin, *Nat. Commun.*, 2020, **11**, 4293–4300.
- 18 (a) D. R. Taylor, *Chem. Rev.*, 1967, **67**, 317–359; (b) *Modern Allene Chemistry Vol. 1*, ed., N. Krause and A. S. K. Hashmi, Wiley-VCH, Weinheim, 2004, DOI: [10.1002/9783527619573](https://doi.org/10.1002/9783527619573); (c) S. Ma, *Chem. Rev.*, 2005, **105**, 2829–2872; (d) X. Pu, X. Qi and J. M. Ready, *J. Am. Chem. Soc.*, 2009, **131**, 10364–10365; (e) F. Cai, X. Pu, X. Qi, V. Lynch, A. Radha and J. M. Ready, *J. Am. Chem. Soc.*, 2011, **133**, 18066–18069; (f) S. Yu and S. Ma, *Angew. Chem., Int. Ed.*, 2012, **51**, 3074–3112; (g) J. Ye and S. Ma, *Acc. Chem. Res.*, 2014, **47**, 989–1000; (h) B. S. Schreiber, M. Son, F. A. Aouane, M. H. Baik and E. M. Carreira, *J. Am. Chem. Soc.*, 2021, **143**, 21705–21712; (i) Y. Wang, S. G. Scrivener, X. D. Zuo, R. Wang, P. N. Palermo, E. Murphy, A. C. Durham and Y. M. Wang, *J. Am. Chem. Soc.*, 2021, **143**, 14998–15004; (j) W. Xu, X. Cong, K. An, S. Lou, Z. Li, M. Nishiura, T. Murahashi and Z. Hou, *Angew. Chem., Int. Ed.*, 2022, **61**, e202210624.
- 19 (a) M. Sugimoto, T. Ohmura, Y. Miyake, S. Mitani, Y. Ito and M. Murakami, *J. Am. Chem. Soc.*, 2003, **125**, 11174–11175; (b) T. Ohmura, H. Taniguchi and M. Sugimoto, *J. Am. Chem. Soc.*, 2006, **128**, 13682–13683.



- 20 M. Kidonakis and M. Stratakis, *ACS Catal.*, 2018, **8**, 1227–1230.
- 21 J. Chen, S. Gao and M. Chen, *Org. Lett.*, 2019, **21**, 8800–8804.
- 22 J. Zhou, Z. Zhao and N. Shibata, *Nat. Commun.*, 2023, **14**, 1847–1855.
- 23 J. P. Barham, G. Coulthard, K. J. Emery, E. Doni, F. Cumine, G. Nocera, M. P. John, E. Leonard, A. Berlouis, T. McGuire, T. Tuttle and J. A. Murphy, *J. Am. Chem. Soc.*, 2016, **138**, 7402–7410.
- 24 (a) D. W. Stephan, *J. Am. Chem. Soc.*, 2015, **137**, 10018–10032; (b) D. Schilter, *Nat. Rev. Chem.*, 2018, **2**, 255; (c) L. L. Liu and D. W. Stephan, *Chem. Soc. Rev.*, 2019, **48**, 3454–3463; (d) F. Holtrop, A. R. Jupp, B. J. Kooij, N. P. Leest and J. C. Slootweg, *Angew. Chem., Int. Ed.*, 2020, **59**, 22210–22216; (e) A. Dasgupta, E. Richards and R. L. Melen, *Angew. Chem., Int. Ed.*, 2021, **60**, 53–65.
- 25 (a) Y. Yu and J. Zhang, *Eur. J. Org. Chem.*, 2022, **2022**, e202201017; (b) L. Liu, R. M. Ward and J. M. Schomaker, *Chem. Rev.*, 2019, **119**, 12422–12490; (c) Q. Liu, J. Zheng, X. Zhang and S. Ma, *Nat. Commun.*, 2022, **13**, 3302–3311.
- 26 H. Saito, K. Nogi and H. Yorimitsu, *Angew. Chem., Int. Ed.*, 2018, **57**, 11030–11034.
- 27 P. Thangsan, T. Rukkijakan, B. Thanaussavadee, K. Yiamsawat, J. Sirijaraensre and P. Gable, *Org. Biomol. Chem.*, 2023, **21**, 1501–1513.
- 28 H. Huang, G. Zhang, L. Gong, S. Zhang and Y. Chen, *J. Am. Chem. Soc.*, 2014, **136**, 2280–2283.
- 29 A. T. Tran, V. A. Huynh, E. M. Friz, S. K. Whitney and D. B. Cordes, *Tetrahedron Lett.*, 2009, **50**, 1817–1819.
- 30 Q. Yang, Y. Li, J. Yang, Y. Liu, L. Zhang, S. Luo and J. Cheng, *Angew. Chem., Int. Ed.*, 2020, **59**, 19282–19291.
- 31 J. Maury, S. Jammie, F. Vibert, S. R. A. Marque, D. Siri, L. Feray and M. Bertrand, *J. Org. Chem.*, 2012, **77**, 9081–9086.
- 32 (a) K. B. Wiberg, *Chem. Rev.*, 1955, **55**, 713–743; (b) S. Kopf, F. Bourriquen, W. Li, H. Neumann, K. Junge and M. Beller, *Chem. Rev.*, 2022, **122**, 6634–6718.
- 33 (a) S. P. Bew, G. D. Hiatt-Gipson, J. A. Lovell and C. Poullain, *Org. Lett.*, 2012, **14**, 456–459; (b) B. Chatterjee and C. Gunanathan, *Chem. Commun.*, 2016, **52**, 4509–4512; (c) W. Xiong, F. Shi, R. Cheng, B. Zhu, L. Wang, P. Chen, H. Lou, W. Wu, C. Qi, M. Lei and H. Jiang, *ACS Catal.*, 2020, **10**, 7968–7978.

