RSC Mechanochemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *RSC Mechanochem.*, 2025, **2**, 256

Direct arylation of *gem*-difluorostyrenes using *in situ* mechanochemically generated calcium-based heavy Grignard reagents†

Xihong Wang,[a] Yamato Fukuzawa,[b] Pan Gao,[a] Julong Jiang,[a] Satoshi Maeda,[ac] Koji Kubota *[ab] and Hajime Ito *[ab]

Received 19th November 2024
Accepted 21st December 2024

DOI: 10.1039/d4mr00135d

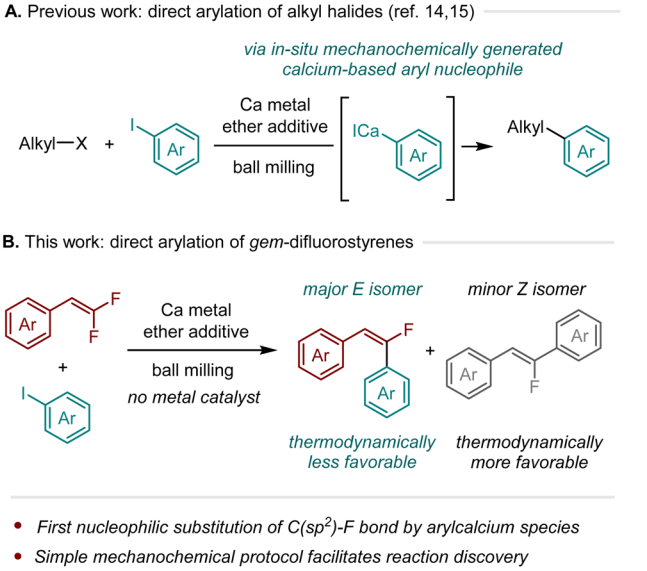
rsc.li/RSCMechanochem

In this study, we disclosed that calcium-based heavy Grignard reagents, prepared *in situ* through a mechanochemical method, reacted with *gem*-difluorostyrenes in the absence of transition-metal catalysts to afford thermodynamically less favorable (*E*)-monofluorostilbenes with good to high stereoselectivity. To the best of our knowledge, this is the first example of nucleophilic substitution of a C(sp^2)–F bond by an arylcalcium compound.

Organocalcium compounds have gained significant attention owing to their unique structures and reactivities.[1–5] However, there has been limited exploration of synthetic applications involving calcium-based carbon nucleophiles.[6] This is largely due to the absence of straightforward and convenient methods for generating these highly reactive nucleophiles from commercially available starting materials, which may hinder a comprehensive investigation of their reactivity profiles.[1–5] As a result, basic reactions involving organocalcium nucleophiles are currently underdeveloped.

Building on this background, we recently developed a straightforward mechanochemical protocol that employs ball milling to generate calcium-based heavy Grignard reagents (R–CaX)[6–13] from unactivated calcium metal.[14–16] Conventionally, such direct synthesis requires the preparation of activated calcium metal, such as Rieke calcium.[10–12] In contrast, our mechanochemical approach employs commercial calcium metal and does not require inert gas protection, simplifying the operating process for the generation of organocalcium nucleophiles.[14,15] This simple protocol is expected to enable synthetic chemists to more easily explore novel reactivities of organocalcium nucleophiles. Indeed, we found that mechanochemically generated aryl calcium species react smoothly with unactivated alkyl halides,[14,15] including alkyl fluorides, in the absence of transition metal catalysts (Scheme 1A).[16,17]

Based on these achievements, particularly the C(sp^3)–F bond arylation by organocalcium compounds,[15] we investigated the feasibility of a direct organocalcium-mediated C(sp^2)–F bond arylation reaction.[18] Herein, we report that calcium-based heavy Grignard reagents, which were mechanochemically generated *in situ*, reacted with *gem*-difluorostyrenes in the absence of transition-metal catalysts to afford thermodynamically less favorable (*E*)-monofluorostilbenes with good to high stereoselectivity (Scheme 1B).[19–28] To the best of our knowledge, this is the first example of nucleophilic substitution of a C(sp^2)–F bond by an arylcalcium compound.[29,30] Furthermore, this represents a rare instance where thermodynamically less favorable stereoisomers are formed from the defluorofunctionalization of



Scheme 1 Discovery of new reactions involving organocalcium compounds by a mechanochemical method.

[a]Institute for Chemical Reaction Design and Discovery (WPI-ICReDD), Hokkaido University, Sapporo, Hokkaido, Japan. E-mail: hajito@eng.hokudai.ac.jp; kbt@eng.hokudai.ac.jp

[b]Division of Applied Chemistry, Faculty of Engineering, Hokkaido University, Sapporo, Hokkaido, Japan

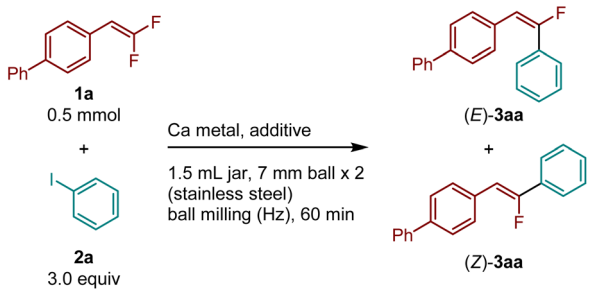
[c]Department of Chemistry, Faculty of Science, Hokkaido University, Sapporo, Hokkaido, Japan

† Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d4mr00135d

gem-difluoroalkenes.[19–28] The utility of this protocol was demonstrated by the stereoselective synthesis of a monofluorinated combretastatin A-4 analog.[31] This study illustrates the effectiveness of a straightforward mechanochemical method for exploring a previously overlooked reactivity of calcium-based heavy Grignard reagents.

Initially, we optimized the conditions of the defluoroarylation of *gem*-difluorostyrene (**1a**) using an *in situ* mechanochemically generated aryl calcium nucleophile (Table 1). All reactions were conducted in a Retsch MM400 mixer mill (stainless-steel milling jar; 30 Hz; stainless-steel balls). Commercially available *gem*-difluorostyrene (**1a**), unactivated calcium metal (1.0 equiv.), and iodobenzene (**2a**, 3.0 eq.) were sequentially weighed in air and added to a 1.5 mL stainless-steel jar along with two 7 mm stainless-steel balls. Upon the addition of tetrahydropyran (THP, 4.0 equiv.), which is an essential additive for the generation of calcium-based aryl nucleophiles,[14,15] the jar was sealed and then placed in a Retsch MM400 mixer mill. After ball milling at 30 Hz for 1 h, (*E*)-monofluorostilbene [(*E*)-**3aa**] was obtained in 60% yield with high stereoselectivity towards the thermodynamically less favorable *E* isomer (*E* : *Z* = 81 : 19) (entry 1).[19] It was found that the use of tetrahydrofuran (THF) instead of THP afforded (*E*)-**3aa** in 68% yield with a slightly higher *E* selectivity (*E* : *Z* = 83 : 17). Notably, the pure *E* isomer of **3aa** (*E* : *Z* = >99 : 1) was isolated by silica gel column chromatography (entry 2). When the milling frequency was reduced to 20 Hz, the yield of **3aa** decreased (entry 3, 58%; *E* : *Z* = 85 : 15). The use of 1.0 equivalent of calcium metal afforded a lower yield (54%) with a slightly increased *E* : *Z* selectivity (entry 4, *E* : *Z* = 86 : 14). The use of 2.0 equivalents of calcium metal significantly decreased both the yield and *E* : *Z* ratio (entry 5, 42% yield, *E* : *Z* = 74 : 26). We also examined the effect of the amount of THF additive (entries 6 and 7). When using 8.0 equivalents of THF, the *E* : *Z* ratio was similar to that of the reaction using 4.0 equivalents (entry 6, *E* : *Z* = 85 : 15), whereas 2.0 equivalents of THF resulted in a poor *E* : *Z* ratio (entry 7, *E* : *Z* ratio = 77 : 23).

Table 1 Optimization of the reaction conditions[a]



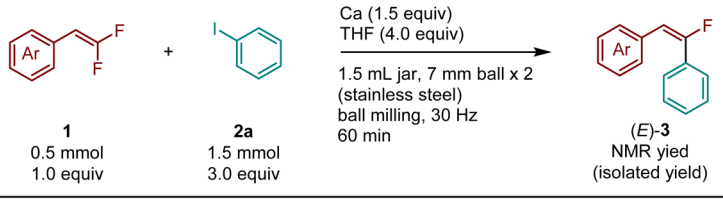
Entry	Equiv. Of Ca	Hz	Additive	Yield[b] of **3aa** (%)	*E* : *Z*[b]
1	1.5	30	THP (4.0 equiv.)	60	81 : 19
2	1.5	30	THF (4.0 equiv.)	68 (45[c,d])	83 : 17
3	1.5	20	THF (4.0 equiv.)	58	85 : 15
4	1.0	30	THF (4.0 equiv.)	54	86 : 14
5	2.0	30	THF (4.0 equiv.)	42	74 : 26
6	1.5	30	THF (8.0 equiv.)	54	85 : 15
7	1.5	30	THF (2.0 equiv.)	56	77 : 23

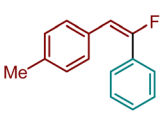
[a] Conditions: **1a** (0.5 mmol), **2a** (1.5 mmol), Ca, and additive in a stainless-steel ball-milling jar (1.5 mL) with two stainless-steel balls (diameter: 7 mm). [b] Yields were determined by ^{1}H NMR spectroscopy using dibromomethane as an internal standard. [c] Isolated yield. [d] After repeated column chromatographic separations, the *E* : *Z* ratio was >99 : 1.

With the optimized conditions in hand, we explored the substrate scope for the defluoroarylation of various *gem*-difluorostyrenes (Table 2). *gem*-Difluorostyrenes containing a methyl group in the *para*, *meta*, and *ortho* positions on the phenyl ring (**1b–1d**) reacted smoothly to afford the corresponding products (**3ba–3da**) in moderate to good yields (60–64%) with high *E* selectivity. Almost pure *E* isomers were obtained *via* purification by either silica gel column chromatography or gel-permeation column chromatography (for details, see ESI†). Substrates bearing *ortho*-substituents such as *tert*-butyl- (**1e**), methoxy- (**1f**), benzyloxy- (**1g**), phenyl- (**1h**), bromo- (**1i**), trifluoromethyl- (**1j**), trifluoromethoxy- (**1k**), or trimethylsilyl- (**1l**) were fully tolerated under defluoroarylation reaction conditions, resulting in the corresponding monofluorostilbene derivatives in moderate to good yields (43–84%) with high *E* selectivity (**3ea–3la**). Naphthalene-containing substrates (**1m** and **1n**) underwent defluoroarylation to form the desired products (**3ma** and **3na**) in good yields (65 and 58%, respectively) with high *E* selectivity. The reactions of substrates bearing *tert*-butyl (**1o**) or diphenylamino (**1p**) groups at the *para* position afforded the desired products (**3oa** and **3pa**) in good yields (68 and 78%, respectively) with high *E* selectivity. A benzo[*b*]thiophene-containing substrate (**1q**) was also converted to the desired product **3qa** with good *E* selectivity (*E* : *Z* = 73 : 27). Interestingly, the reaction of 1-bromo-4-(1,1-difluoroprop-1-en-2-yl)benzene (**1r**) afforded (*Z*)-**3ra** as the major isomer (*E* : *Z* = 33 : 67) in high yield (76%). Unfortunately, 2-(2,2-difluorovinyl)-1,3,5-trimethylbenzene (**1s**), which contains two methyl groups at *ortho* position of the phenyl ring, afforded only an 11% yield of **3sa** with good *Z* selectivity (*E* : *Z* = 26 : 74). It should be noted that the relatively low isolated yields compared to their NMR yields were primarily due to the difficulty of separating the *E* and *Z* arylated products. To isolate stereochemically pure *E* products, we performed multiple rounds of purification using silica gel column chromatography and gel-permeation chromatography. However, this process led to relatively low isolated yields of the desired *E* products.

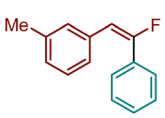
Subsequently, the reactions were investigated using various aryl iodides (Table 3). We found that 1-iodonaphthalene (**2b**), *o*-isopropyl- (**2c**)-, and *o*-methyl- (**2d**)-substituted iodobenzene derivatives furnished the desired products (**3ab–3ad**) in high yields (69–76%) with high *E* stereoselectivity. However, separation of the *E*/*Z* isomers by silica gel chromatography proved challenging in these cases. Methyl groups at different positions did not significantly affect the reactivity and selectivity (**3ae**: 60%, *E* : *Z* = 84 : 16, **3af**: 71%, *E* : *Z* = 87 : 13). Aryl iodides bearing either electron-withdrawing or electron-donating substituents at the *para* position and two methyl groups at the *meta* position were also suitable for this reaction (**3ag–3am**).

Table 2 Substrate scope of *gem*-difluorostyrenes[a]

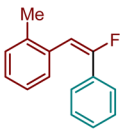




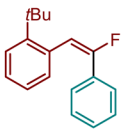
(*E*)-**3ba**
64%, *E*:*Z* 87:13
(36%, *E*:*Z* 98:2)



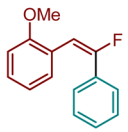
(*E*)-**3ca**
60%, *E*:*Z* 82:18
(35%, *E*:*Z* >99:1)



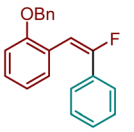
(*E*)-**3da**
64%, *E*:*Z*: 87:13
(40%, *E*:*Z*: >99:1)



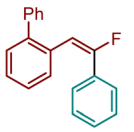
(*E*)-**3ea**
64%, *E*:*Z* 87:13
(38%, *E*:*Z* >99:1)



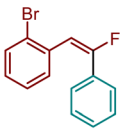
(*E*)-**3fa**
62%, *E*:*Z* 85:15
(48%, *E*:*Z* 84:16)



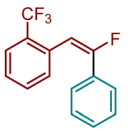
(*E*)-**3ga**
71%, *E*:*Z* 84:16
(59%, *E*:*Z* 83:17)



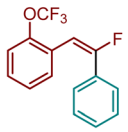
(*E*)-**3ha**
80%, *E*:*Z* 78:22
(47%, *E*:*Z* 79:21)



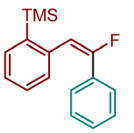
(*E*)-**3ia**
43%, *E*:*Z* 91:9
(31%, *E*:*Z* 89:11)



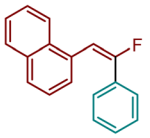
(*E*)-**3ja**
48%, *E*:*Z* 89:11
(24%, *E*:*Z* 97:3)



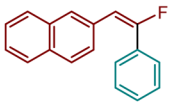
(*E*)-**3ka**
58%, *E*:*Z* 84:16
(41%, *E*:*Z* >99:1)



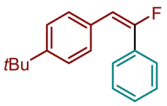
(*E*)-**3la**
84%, *E*:*Z* 90:10
(80%, *E*:*Z* 90:10)



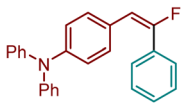
(*E*)-**3ma**
65%, *E*:*Z* 84:16
(47%, *E*:*Z* >99:1)



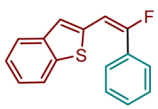
(*E*)-**3na**
58%, *E*:*Z* 86:14
(26%, *E*:*Z* >99:1)



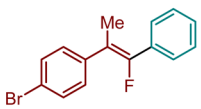
(*E*)-**3oa**
68%, *E*:*Z* 81:19
(40%, *E*:*Z* 93:7)



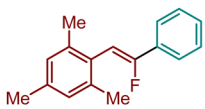
(*E*)-**3pa**
78%, *E*:*Z* 86:14
(74%, *E*:*Z* 87:13)



(*E*)-**3qa**
48%, *E*:*Z* 73:27
(24%, *E*:*Z* >99:1)



(*Z*)-**3ra**
76%, *E*:*Z* 33:67
(34%, *Z*:*E* >99:1)



(*Z*)-**3sa**
11%, *E*:*Z* 26:74
coversion of **1s** : 44%

[a] Reaction conditions: *gem*-difluoroalkene **1** (0.5 mmol, 1.0 equiv.), iodobenzene **2a** (1.5 mmol, 3.0 equiv.), Ca (0.75 mmol, 1.5 equiv.), THF (4.0 mmol) in a stainless-steel ball-milling jar (1.5 mL) with two stainless-steel balls (diameter: 7 mm), ball milling (30 Hz) for 1 h. ^{1}H NMR yields are shown. Isolated yields are shown in parentheses. The *E*/*Z* ratio was determined by ^{19}F NMR analysis.

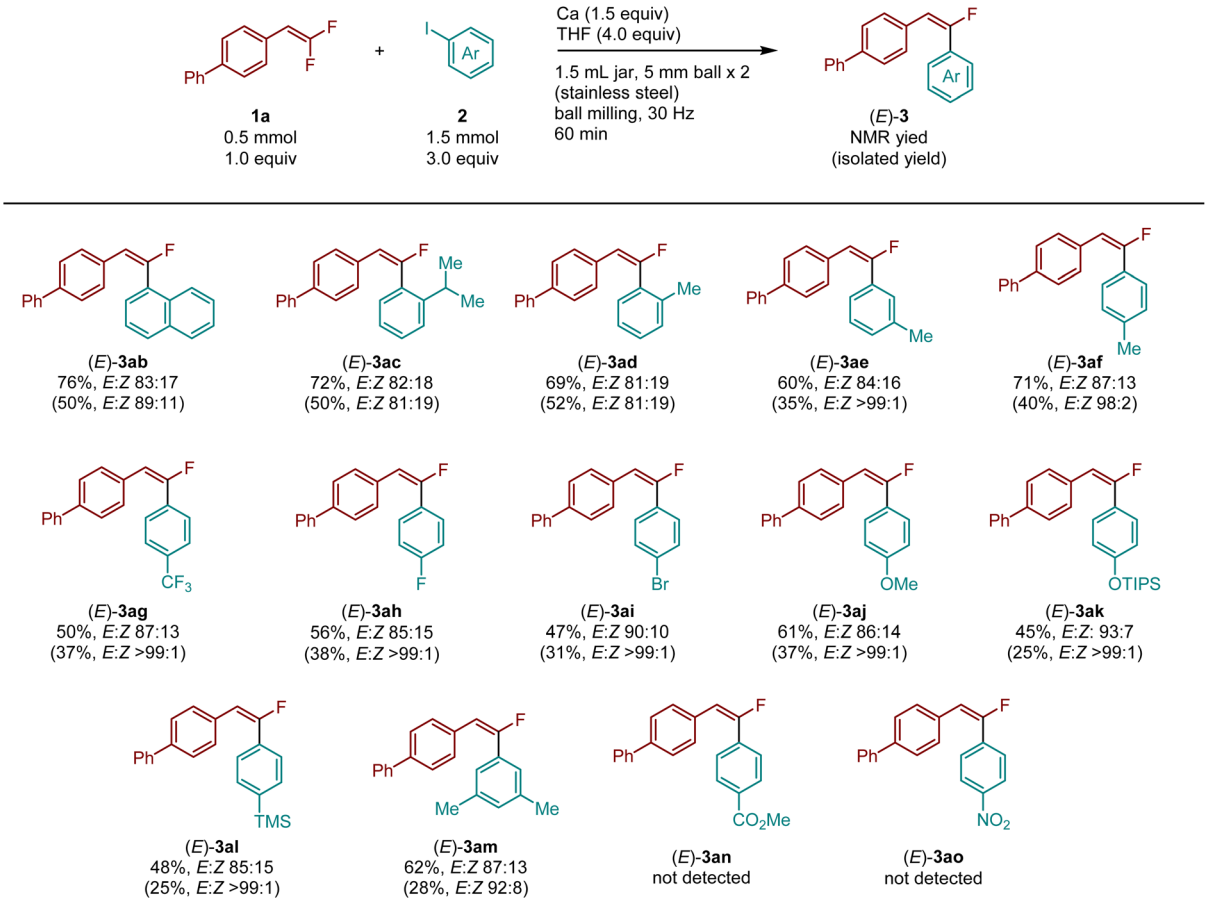
Unfortunately, ester and nitro groups were incompatible under these conditions.

To demonstrate the potential applicability of this method to the synthesis of bioactive compounds, we synthesized a monofluorinated combretastatin A-4 analogue [(*E*)-**3tp**] with anticancer activity (Scheme 2).[31] The reaction between 5-(2,2-difluorovinyl)-1,2,3-trimethoxybenzene (**1t**) and 2-fluoro-4-iodo-1-methoxybenzene (**2p**) in the presence of calcium metal furnished the desired product **3tq** with excellent *E* selectivity. Pure (*E*)-**3tq** was obtained by flash silica gel chromatography.

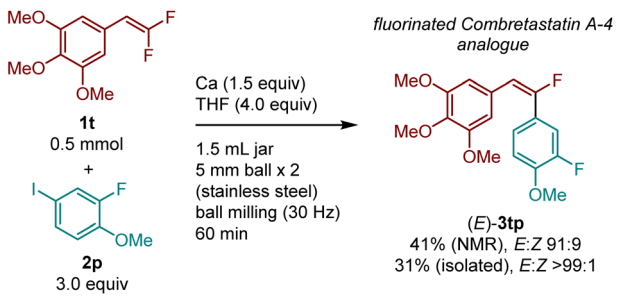
Next, the reaction using Rieke calcium under solution-based conditions was investigated to obtain a mechanistic insight (Scheme 3). The Rieke method using lithium biphenylide was employed to generate the corresponding aryl calcium species from **2a**, and the desired product (*E*)-**3aa** was obtained with high stereoselectivity (21%, $E:Z = 89:11$). This result suggests that the C(sp^2)–F bond arylation under mechanochemical conditions most likely occurs through the selective formation of aryl calcium nucleophiles *via* direct insertion of calcium metal into a C(sp^2)–I bond, followed by defluoroarylation of a *gem*-difluorostyrene. At this stage, the detailed mechanism of the nucleophilic substitution of the C(sp^2)–F bond remains unclear.

Next, we tested the defluoroarylation reaction using conventional Grignard reagents (Scheme 4). Cao *et al.* previously reported the defluoroalkylation of *gem*-difluorostyrenes using bulky alkyl Grignard reagents in the absence of transition-metal catalysts to form thermodynamically more stable *Z* stereoisomers. In contrast, the use of sterically less hindered primary alkyl Grignard reagents afforded *E*/*Z* mixtures (Scheme 4A).[26] Interestingly, it was found that the use of a THF solution

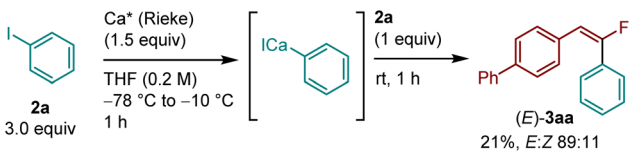
Table 3 Substrate scope of aryl iodides[a]



[a] Reaction conditions: *gem*-difluoroalkene **1** (0.5 mmol, 1.0 equiv.), iodobenzene **2a** (1.5 mmol, 3.0 equiv.), Ca (0.75 mmol, 1.5 equiv.), THF (4.0 mmol) in a stainless-steel ball-milling jar (1.5 mL) with two stainless-steel balls (diameter: 7 mm), ball milling (30 Hz) for 1 h. ^{1}H NMR yields are shown. Isolated yields are shown in parentheses. The *E*/*Z* ratio was determined by ^{19}F NMR analysis.



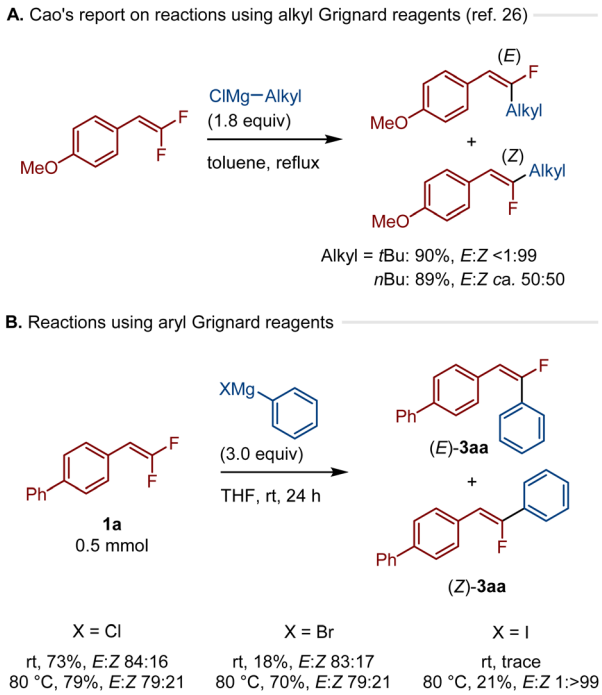
Scheme 2 Synthesis of fluorinated Combretastatin A-4 analog (*E*)-**3tp** *via* *E*-selective defluoroarylation using a calcium-based heavy Grignard reagent. The details of the conditions are shown in the ESI.†



Scheme 3 Reaction using Rieke calcium in solution. The details of the conditions are shown in the ESI.†

of Ph–MgCl in the defluoarylation of **1a** at room temperature led to thermodynamically less stable (*E*)-**3aa** in 73% yield with high stereoselectivity ($E:Z = 84:16$) (Scheme 4B). The reaction with Ph–MgBr also exhibited the *E* selectivity, however, the product yield was low ($E:Z = 81:19$, 18%). When these reactions were carried out at 80 °C, the yields were improved while the *E* selectivity was slightly decreased (Cl: $E:Z = 79:21$, 79%, Br: $E:Z = 79:21$, 70%). Interestingly, excellent *Z* selectivity was obtained when Ph–MgI was used at 80 °C ($E:Z = 1:>99$, 21%). Overall, these results show that the *E* stereoselectivity is not unique to calcium-based heavy Grignard reagents. In the case of traditional Grignard reagents, the stereoselectivity of this transformation is highly sensitive to the choice of organic groups (alkyl or aryl) and halides on magnesium.

In conclusion, we found a new reaction between calcium-based heavy Grignard reagents, which were generated *in situ* *via* a simple mechanochemical method, and *gem*-difluorostyrenes in the absence of transition-metal catalysts, resulting in



Scheme 4 Reactions using Grignard reagents in solution. The details of the conditions are shown in the ESI.†

moderate to high yields of the corresponding C(sp^2)–F bond arylation products with good to high stereoselectivity. Notably, this is the first reported instance of an arylcalcium species engaging in nucleophilic substitution of a C(sp^2)–F bond. These findings confirm that our operationally simple mechanochemical protocol using commercial calcium metal provides a valuable platform for discovering new reactions involving calcium-based carbon nucleophiles. Further studies to elucidate the mechanism of the C(sp^2)–F bond substitution reaction as well as the observed stereoselectivity are ongoing in our laboratory.

Data availability

The data supporting this article have been included as part of the ESI.†

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was financially supported by the Japan Society for the Promotion of Science (JSPS) *via* the KAKENHI grants 22H00318, 22K18333, 24H00453, 24H01832, and 24H01050; by the JST *via* the CREST grant JPMJCR19R1 and FOREST grant JPMJFR201I; and by the Institute for Chemical Reaction Design and Discovery (ICReDD) established by the World Premier International Research Initiative (WPI), MEXT, Japan. We thank Ms. Hina Shoji for her help with cross-checking the experiments.

Notes and references

1 For selected reviews on organocalcium chemistry, see(*a*) T. P. Hanusa, *Chem. Rev.*, 1993, **93**, 1023; (*b*) M. Westerhausen, *Angew. Chem., Int. Ed.*, 2001, **40**, 2975; (*c*) J. S. Alexander, *Eur. J. Inorg. Chem.*, 2002, **2002**, 2761.

2 Selected examples and reviews of the reactions using organocalcium compounds as catalysts:(*a*) S. Harder, *Chem. Rev.*, 2010, **110**, 3852; (*b*) S. Kobayashi and Y. Yamashita, *Acc. Chem. Res.*, 2011, **44**, 58; (*c*) M. S. Hill, D. J. Liptrota and C. Weetman, *Chem. Soc. Rev.*, 2016, **45**, 972; (*d*) M. Magre, S. Marcin and M. Rueping, *Chem. Rev.*, 2022, **122**, 8261; (*e*) L. Zhao, P. Deng, X. Gong, X. Kang and J. Cheng, *ACS Catal.*, 2022, **12**, 7877.

3 Selected examples of reactions using organocalcium compounds as carbon nucleophiles:(*a*) A. S. Wilson, M. S. Hill, M. F. Mahon, C. Dinoi and L. Maron, *Science*, 2017, **358**, 1168; (*b*) B. M. Wolf, C. Stuhl, C. Maichle-Mössmer and R. Anwander, *J. Am. Chem. Soc.*, 2018, **140**, 2373.

4 Selected examples of organocalcium-mediated polymerization are as follows: (*a*) S. Harder, F. Feil and A. Weeber, *Organometallics*, 2001, **20**, 1044; (*b*) S. Harder and F. Feil, *Organometallics*, 2002, **21**, 2268; (*c*) M. Westerhausen, S. Schneiderbauer, A. N. Kneifel, Y. Söltl, P. Mayer, H. Nöth, Z. Zhong, P. J. Dijkstra and J. Feijen, *Eur. J. Inorg. Chem.*, 2003, **2003**, 3432; (*d*) Y. Li, H. Deng, W. Brittain and M. S. Chisholm, *Polym. Bull.*, 1999, **42**, 635; (*e*) M.-W. Hsiao and C.-C. Lin, *Dalton Trans.*, 2013, **42**, 2041.

5 Selected reviews of calcium-based heavy Grignard reagents: (*a*) M. Westerhausen, M. Gärtner, R. Fischer, J. Langer, L. Yu and M. Reiher, *Chem.–Eur. J.*, 2007, **13**, 6292; (*b*) M. Westerhausen, M. Gärtner, R. Fischer and J. Langer, *Angew. Chem., Int. Ed.*, 2007, **46**, 1950; (*c*) M. Westerhausen, *Coord. Chem. Rev.*, 2008, **252**, 1516; (*d*) M. Westerhausen, A. Koch, H. Görls and S. Krieck, *Chem.–Eur. J.*, 2017, **23**, 1456; (*e*) A. Koch, Q. Dufrois, M. Wirgenings, H. Görls, S. Krieck, M. Etienne, G. Pohnert and M. Westerhausen, *Chem.–Eur. J.*, 2018, **24**, 16840; (*f*) S. Harder and J. Langer, *Nat. Rev. Chem*, 2023, **7**, 843; (*g*) P. Schüler, S. Sengupta, S. Krieck and M. Westerhausen, *Chem.–Eur. J.*, 2023, **29**, e202300833.

6 (*a*) *Organometallics in Synthesis: A Manual*, ed. M. Schlosser, Wiley, Chester, 2nd edn, 2013; (*b*) T. Banno, Y. Hayakawa and M. Umeno, *J. Organomet. Chem.*, 2002, **653**, 288; (*c*) *Handbook of Grignard Reagents*, ed. G. S. Silverman and P. E. Rakita, Marcel Dekker, 1996; (*d*) *The Chemistry of Organozinc Compounds*, ed. Z. Rappoport and I. Marek, John Wiley & Sons, Chichester, U.K., 2006; (*e*) U. Wietelmann and J. Klett, *Z. Anorg. Allg. Chem.*, 2018, **644**, 194.

7 (*a*) M. Gärtner, H. Görls and M. Westerhausen, *Organometallics*, 2007, **26**, 1077; (*b*) M. Gärtner, H. Görls and M. Westerhausen, *J. Organomet. Chem.*, 2008, **693**, 221; (*c*) M. Westerhausen, *Angew. Chem., Int. Ed.*, 2009, **48**, 5741;

(*d*) J. Langer, M. Köhler, H. Görls and M. Westerhausen, *Chem.–Eur. J.*, 2014, **20**, 3154.

8 (*a*) R. Fischer, M. Gärtner, H. Görls, L. Yu, M. Reiher and M. Westerhausen, *Angew. Chem., Int. Ed.*, 2007, **46**, 1618; (*b*) P. Schüler, S. Sengupta, A. Koch, H. Görls, S. Krieck and M. Westerhausen, *Chem.–Eur. J.*, 2022, **28**, e202201897; (*c*) P. Schüler, S. Sengupta, S. Krieck and M. Westerhausen, *Chem.–Eur. J.*, 2023, **29**, e20230083.

9 A. Koch, M. Wirgenings, S. Krieck, H. Görls, G. Pohnert and M. Westerhausen, *Organometallics*, 2017, **36**, 3981.

10 (*a*) T.-C. Wu, H. Xiong and R. D. Rieke, *J. Org. Chem.*, 1990, **55**, 5045; (*b*) K. Mochida and H. Ogawa, *J. Organomet. Chem.*, 1983, **243**, 131; (*c*) R. D. Rieke, T.-C. Wu and L. I. Rieke, *Org. Synth.*, 1995, **72**, 147; (*d*) D. Bryce-Smith and A. C. Skinner, *J. Chem. Soc.*, 1963, 577; (*e*) M. L. Hays and T. P. Hanusa, *Tetrahedron Lett.*, 1995, **36**, 2435.

11 J. Langer, M. Köhler, H. Görls and M. Westerhausen, *J. Organomet. Chem.*, 2014, **751**, 563.

12 (*a*) R. Fischer, M. Gärtner, H. Görls and M. Westerhausen, *Organometallics*, 2006, **25**, 3496; (*b*) M. Gärtner, H. Görls and M. Westerhausen, *Synthesis*, 2007, 725; (*c*) M. Westerhausen, M. Gärtner, R. Fischer and J. Langer, *Angew. Chem., Int. Ed.*, 2007, **46**, 1950; (*d*) N. Kawabata, A. Matsumura and S. Yamashita, *Tetrahedron*, 1973, **29**, 1069.

13 (*a*) M. Köhler, J. Langer, H. Görls and M. Westerhausen, *Organometallics*, 2014, **33**, 6381; (*b*) M. Gärtner, H. Görls and M. Westerhausen, *J. Organomet. Chem.*, 2008, **693**, 221.

14 P. Gao, J. Jiang, S. Maeda, K. Kubota and H. Ito, *Angew. Chem., Int. Ed.*, 2022, **61**, e202207118.

15 P. Gao, J. Jiang, Y. Fukuzawa, S. Maeda, K. Kubota and H. Ito, *RSC Mechanochem.*, 2024, **1**, 486.

16 For selected reviews on reaction development using mechanochemistry, see:(*a*) S. L. James, C. J. Adams, C. Bolm, D. Braga, P. Collier, T. Friščić, F. Grepioni, K. D. M. Harris, G. Hyett, W. Jones, A. Krebs, J. Mack, L. Maini, A. G. Orpen, I. P. Parkin, W. C. Shearouse, J. W. Steed and D. C. Waddell, *Chem. Soc. Rev.*, 2012, **41**, 413; (*b*) G.-W. Wang, *Chem. Soc. Rev.*, 2013, **42**, 7668; (*c*) J.-L. Do and T. Friščić, *ACS Cent. Sci.*, 2017, **3**, 13; (*d*) J. G. Hernández and C. Bolm, *J. Org. Chem.*, 2017, **82**, 4007; (*e*) J. G. Hernández, *Chem.–Eur. J.*, 2017, **23**, 17157; (*f*) T. K. Achar, A. Bose and P. Mal, *Beilstein J. Org. Chem.*, 2017, **13**, 1907; (*g*) J.-L. Do and T. Friščić, *Synlett*, 2017, **28**, 2066; (*h*) D. Tan and T. Friščić, *Eur. J. Org Chem.*, 2018, **18**, 18; (*i*) J. L. Howard, Q. Cao and D. L. Browne, *Chem. Sci.*, 2018, **9**, 3080; (*j*) J. Andersen and J. Mack, *Green Chem.*, 2018, **20**, 1435; (*k*) N. R. Rightmire and T. P. Hanusa, *Dalton Trans.*, 2016, **45**, 2352; (*l*) M. Leonardi, M. Villacampa and J. C. Menéndez, *Chem. Sci.*, 2018, **9**, 2042; (*m*) D. Tan, L. Loots and T. Friščić, *Chem. Commun.*, 2016, **52**, 7760; (*n*) D. Tan and F. García, *Chem. Soc. Rev.*, 2019, **48**, 2274; (*o*) C. Bolmm and J. G. Hernández, *Angew. Chem., Int. Ed.*, 2019, **58**, 3285; (*p*) T. Friščić, C. Mottillo and H. M. Titi, *Angew. Chem., Int. Ed.*, 2020, **59**, 1018; (*q*) I. N. Egorov, S. Santra, D. S. Kopchuk, I. S. Kovalev, G. V. Zyryanov, A. Majee, B. C. Ranu, V. L. Rusinov and O. N. Chupakhin, *Green Chem.*, 2020, **22**, 302; (*r*) A. Pocheddu, E. Colacino, L. De Luca and F. Delogu, *ACS Catal.*, 2020, **10**, 8344; (*s*) K. Kubota and H. Ito, *Trends Chem.*, 2020, **2**, 1066; (*t*) P. Ying, J. Yu and W. Su, *Adv. Synth. Catal.*, 2021, **363**, 1246; (*u*) K. J. Ardila-Fierro and J. G. Hernández, *ChemSusChem*, 2021, **14**, 2145; (*v*) V. Martinez, T. Stolar, B. Karadeniz, I. Brekalo and K. Užarević, *Nat. Rev. Chem*, 2023, **7**, 51; (*w*) N. Fantozzi, J.-N. Volle, A. Porcheddu, D. Virieux, F. García and E. Colacino, *Chem. Soc. Rev.*, 2023, **52**, 6680; (*x*) K. Kubota, *Bull. Chem. Soc. Jpn.*, 2023, **96**, 913.

17 Selected examples of transition-metal-free nucleophilic substitution of alkyl fluorides using organometallic reagents: (*a*) K. Matsubara, T. Ishibashi and Y. Koga, *Org. Lett.*, 2009, **11**, 1765; (*b*) J. Terao, S. A. Begum, Y. Shinohara, M. Tomita, Y. Naitoh and N. Kambe, *Chem. Commun.*, 2007, 855; (*c*) L. Kane, B. C. Figula, K. Balaraman, J. A. Bertke and C. Wolf, *Nat. Commun.*, 2024, **15**, 1866.

18 For selected reviews on C–F bond activation in organic synthesis, see: (*a*) H. Amii and K. Uneyama, *Chem. Rev.*, 2009, **109**, 2119; (*b*) J.-D. Hamel and J.-F. Paquin, *Chem. Commun.*, 2018, **54**, 10224; (*c*) T. Stahl, H. F. T. Klare and M. Oestreich, *ACS Catal.*, 2013, **3**, 1578; (*d*) G. Coates, F. Rekhroukh and M. R. Crimmin, *Synlett*, 2019, **30**, 2233; (*e*) T. Ahrens, J. Kohlmann, M. Ahrens and T. Braun, *Chem. Rev.*, 2015, **115**, 931; (*f*) Q. Shen, Y.-G. Huang, C. Liu, J.-C. Xiao, Q.-Y. Chen and Y. Guo, *J. Fluorine Chem.*, 2015, **179**, 14.

19 DFT calculations [B3LYP-D3/6-311G(d,p)//B3LYP-D3/6-311G(d,p)] revealed that (*Z*)-**3a** is thermodynamically more stable than (*E*)-**3a** by 15.0 kJ mol^{-1}.

20 Reviews on the synthesis and applications of monofluoroalkenes:(*a*) S. Oishi, H. Kamitani, Y. Kodera, K. Watanabe, K. Kobayashi, T. Narumi, K. Tomita, H. Ohno, T. Naito, E. Kodama, M. Matsuoka and N. Fuji, *Org. Biomol. Chem.*, 2009, **7**, 2872; (*b*) H. Yanai and T. Taguchi, *Eur. J. Org Chem.*, 2011, **2011**, 5939; (*c*) G. Landelle, M. Bergeron, M.-O. Turcotte-Savard and J.-F. Paquin, *Chem. Soc. Rev.*, 2011, **40**, 2867; (*d*) M. Drouin, J.-D. Hamel and J.-F. Paquin, *Synthesis*, 2018, **50**, 881; (*e*) A. Niida and N. Fujii, *Org. Lett.*, 2006, **8**, 613.

21 Transition-metal-catalyzed direct defluoroarylation of *gem*-difluorostyrenes to form (*Z*)-monofluorostilbenes: (*a*) R. T. Richard and F. D. Toste, *Angew. Chem., Int. Ed.*, 2016, **55**, 11629; (*b*) Y. Xiong, T. Huang, X. Ji, J. Wu and S. Cao, *Org. Biomol. Chem.*, 2015, **13**, 7389; (*c*) P. Tian, C. Feng and T.-P. Loh, *Nat. Commun.*, 2015, **6**, 7472.

22 Stepwise synthesis of (*Z*)-monofluorostilbenes *via* borylation/palladium-catalyzed cross-coupling methodology: (*a*) H. Sakaguchi, Y. Uetake, M. Ohashi, T. Niwa, S. Ogoshi and T. Hosoya, *J. Am. Chem. Soc.*, 2017, **139**, 12855; (*b*) J. Zhang, W. Dai, Q. Liu and S. Cao, *Org. Lett.*, 2017, **19**, 3283.

23 Stepwise synthesis of (*Z*)-monofluorostilbenes *via* defluoroarylation/palladium-catalyzed cross-coupling:

S. Porey, Y. Bairagi, S. Guin, X. Zhang and D. Maiti, *ACS Catal.*, 2023, **13**, 14000.

24 Silyl-group-directed stereoselective synthesis of tri- and tetrasubstituted fluoroalkenes: G. Landelle, P. A. Champagne, X. Barbeau and J.-F. Paquin, *Org. Lett.*, 2009, **11**, 681.

25 Wittig reaction with α-fluorobenzylphosphonium salt to give (*E*)-monofluorostilbenes: D. Mandal, R. Gupta and R. D. Young, *J. Am. Chem. Soc.*, 2018, **140**, 10682.

26 Direct defluoroalkylation of *gem*-difluorostyrenes using Grignard reagents to form *Z*-monofluoroalkenes: W. Dai, H. Shi, X. Zhao and S. Cao, *Org. Lett.*, 2016, **18**, 4284.

27 Palladium-catalyzed chelation-assisted arylation of ester-substituted *gem*-difluoroalkenes: (*a*) Y. Wang, X. Qi, Q. Ma, P. Liu and G. C. Tsui, *ACS Catal.*, 2021, **11**, 4799; (*b*) Y. Wang and G. C. Tsui, *Org. Lett.*, 2024, **26**, 5822.

28 Selected examples of stereoselective functionalization of ester-substituted *gem*-difluoroalkenes: (*a*) M. Li, Y. Wang and G. C. Tsui, *Org. Lett.*, 2021, **23**, 8072; (*b*) Q. Ma, Y. Wang and G. C. Tsui, *Angew. Chem., Int. Ed.*, 2020, **59**, 11293; (*c*) Z. Luo, Y. Zong and G. C. Tsui, *Org. Lett.*, 2023, **25**, 4406; (*d*) Y. Wang, Y. Tang, Y. Zong and G. C. Tsui, *Org. Lett.*, 2022, **24**, 4087.

29 An example of intramolecular aromatic C(sp^2)–F bond alkenylation using alknenyl calcium species: H. Li, X.-Y. Wang, B. Wei, L. Xu, W.-X. Zhang, J. Pei and Z. Xi, *Nat. Commun.*, 2014, **5**, 4508.

30 An example of direct arylation of an aromatic C(sp^2)–Br bond using aryl calcium nucleophiles: K. G. Pearce, C. Dinoi, M. S. Hill, M. F. Mahon, L. Maron, R. S. Schwamm and A. S. S. Wilson, *Angew. Chem., Int. Ed.*, 2022, **61**, e202200305.

31 D. Alloatti, G. Giannini, W. Cabri, I. Lustrati, M. Marzi, A. Ciacci, G. Gallo, M. O. Tinti, M. Marcellini, T. Riccioni, M. B. Guglielmi, P. Carminati and C. Pisano, *J. Med. Chem.*, 2008, **51**, 2708.