# RSC Mechanochemistry



## **PAPER**

View Article Online
View Journal | View Issue



Cite this: RSC Mechanochem., 2025, 2,

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

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Received 19th November 2024 Accepted 21st December 2024

DOI: 10.1039/d4mr00135d

rsc.li/RSCMechanochem

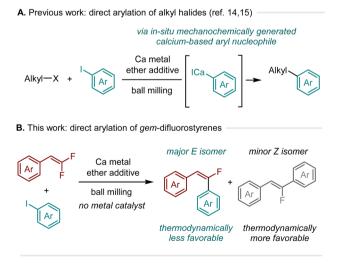
In this study, we disclosed that calcium-based heavy Grignard reagents, prepared *in situ* through a mechanochemical method, reacted with gem-difluorostyrenes in the absence of transition-metal catalysts to afford thermodynamically less favorable (E)-monofluorostilbenes with good to high stereoselectivity. 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.<sup>1-5</sup> However, there has been limited exploration of synthetic applications involving calcium-based carbon nucleophiles.<sup>6</sup> 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.<sup>1-5</sup> 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)<sup>6-13</sup> from unactivated calcium metal.<sup>14-16</sup> Conventionally, such direct synthesis requires the preparation of activated calcium metal, such as Rieke calcium.<sup>10-12</sup> 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.<sup>14,15</sup> 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, <sup>14,15</sup> including alkyl fluorides, in the absence of transition metal catalysts (Scheme 1A).<sup>16,17</sup>

Based on these achievements, particularly the  $C(sp^3)$ –F bond arylation by organocalcium compounds, <sup>15</sup> we investigated the feasibility of a direct organocalcium-mediated  $C(sp^2)$ –F bond arylation reaction. <sup>18</sup> 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). <sup>19–28</sup> 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. <sup>29,30</sup> Furthermore, this represents a rare instance where thermodynamically less favorable stereoisomers are formed from the defluorofunctionalization of

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



- First nucleophilic substitution of C(sp<sup>2</sup>)-F bond by arylcalcium species
- Simple mechanochemical protocol facilitates reaction discovery

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

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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). 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

Table 1 Optimization of the reaction conditions<sup>a</sup>

Entry	Equiv. Of Ca	Hz	Additive	Yield <sup>b</sup> of $3aa$ (%)	$E: Z^b$
		2.0	mrrp (4.0 ' )	50	04.40
1	1.5	30	THP (4.0 equiv.)		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

<sup>&</sup>lt;sup>a</sup> 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). <sup>b</sup> Yields were determined by <sup>1</sup>H NMR spectroscopy using dibromomethane as an internal standard. c Isolated yield. <sup>d</sup> After repeated column chromatographic separations, the E:Z ratio was >99:1.

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).

With the optimized conditions in hand, we explored the substrate scope for the defluoroarylation of various gemdifluorostyrenes (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 tertbutyl- (1e), methoxy- (1f), benzyloxy- (1g), phenyl- (1h), bromo-(1i), trifluoromethyl- (1j), trifluoromethoxy- (1k), or trimethylsilyl- (11) were fully tolerated under defluoroarylation reacconditions. 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 (10) 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 Eproducts, 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), oisopropyl- (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<sup>a</sup>

		Ca (1.5 equiv) THF (4.0 equiv)  1.5 mL jar, 7 mm to (stainless steel) ball milling, 30 Hz 60 min	oall x 2  Ar  (E)-3  NMR yied (isolated yield)	
Me	Me	Me	/Bu F	OMe F
( <i>E</i> )- <b>3ba</b> 64%, <i>E</i> : <i>Z</i> 87:13 (36%, <i>E</i> : <i>Z</i> 98:2)	( <i>E</i> )- <b>3ca</b> 60%, <i>E</i> : <i>Z</i> 82:18 (35%, <i>E</i> : <i>Z</i> >99:1)	( <i>E</i> )- <b>3da</b> 64%, <i>E</i> : <i>Z</i> : 87:13 (40%, <i>E</i> : <i>Z</i> : >99:1)	( <i>E</i> )- <b>3ea</b> 64%, <i>E</i> : <i>Z</i> 87:13 (38%, <i>E</i> : <i>Z</i> >99:1)	( <i>E</i> )- <b>3fa</b> 62%, <i>E</i> : <i>Z</i> 85:15 (48%, <i>E</i> : <i>Z</i> 84:16)
OBn F	Ph	Br	CF <sub>3</sub>	OCF <sub>3</sub>
( <i>E</i> )- <b>3ga</b> 71%, <i>E</i> : <i>Z</i> 84:16 (59%, <i>E</i> : <i>Z</i> 83:17)	( <i>E</i> )- <b>3ha</b> 80%, <i>E:Z</i> 78:22 (47%, <i>E:Z</i> 79:21)	( <i>E</i> )- <b>3ia</b> 43%, <i>E</i> : <i>Z</i> 91:9 (31%, <i>E</i> : <i>Z</i> 89:11)	( <i>E</i> )- <b>3ja</b> 48%, <i>E</i> : <i>Z</i> 89:11 (24%, <i>E</i> : <i>Z</i> 97:3)	( <i>E</i> )- <b>3ka</b> 58%, <i>E</i> : <i>Z</i> 84:16 (41%, <i>E</i> : <i>Z</i> >99:1)
TMS	F	F	<sub>fBu</sub> F	Ph N Ph
( <i>E</i> )- <b>3la</b> 84%, <i>E</i> : <i>Z</i> 90:10 (80%, <i>E</i> : <i>Z</i> 90:10)	( <i>E</i> )- <b>3ma</b> 65%, <i>E</i> : <i>Z</i> 84:16 (47%, <i>E</i> : <i>Z</i> >99:1)	( <i>E</i> )- <b>3na</b> 58%, <i>E</i> : <i>Z</i> 86:14 (26%, <i>E</i> : <i>Z</i> >99:1)	( <i>E</i> )- <b>3oa</b> 68%, <i>E</i> : <i>Z</i> 81:19 (40%, <i>E</i> : <i>Z</i> 93:7)	( <i>E</i> )- <b>3pa</b> 78%, <i>E</i> : <i>Z</i> 86:14 (74%, <i>E</i> : <i>Z</i> 87:13)
	S F	Br F	Me Me Me F	
	( <i>E</i> )- <b>3qa</b> 48%, <i>E:Z</i> 73:27 (24%, <i>E:Z</i> >99:1)	( <i>Z</i> )- <b>3ra</b> 76%, <i>E</i> : <i>Z</i> 33:67 (34%, <i>Z</i> : <i>E</i> >99:1)	( <i>Z</i> ) <b>-3sa</b> 11%, <i>E:Z</i> 26:74 coversion of <b>1s</b> : 44%	

<sup>&</sup>lt;sup>a</sup> 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. <sup>1</sup>H NMR yields are shown. Isolated yields are shown in parentheses. The E/Z ratio was determined by <sup>19</sup>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-(2,2difluorovinyl)-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.

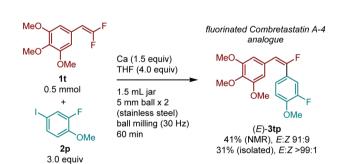
Next, the reaction using Rieke calcium under solution-based conditions was investigated to obtain a mechanistic insight (Scheme 3). The Rieke method using lithium biphenylide was employed to generate the corresponding aryl calcium species from 2a, and the desired product (E)-3aa was obtained with high

stereoselectivity (21%, E: Z = 89:11). This result suggests that the C(sp<sup>2</sup>)-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<sup>2</sup>)-I bond, followed by defluoroarylation of a gemdifluorostyrene. 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 transitionmetal 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<sup>a</sup>

<sup>a</sup> 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 <sup>19</sup>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.†

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

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

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 calciumbased 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



Alkyl = *t*Bu: 90%, *E*:*Z* <1:99 *n*Bu: 89%, *E*:*Z* ca. 50:50

B. Reactions using aryl Grignard reagents

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 calciumbased 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.  $\dot{\uparrow}$ 

### 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.

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