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Silver-Assisted Difunctionalization of Terminal Alkynes: Highly Regio- and Stereoselective Synthesis of Bromofluoroalkenes

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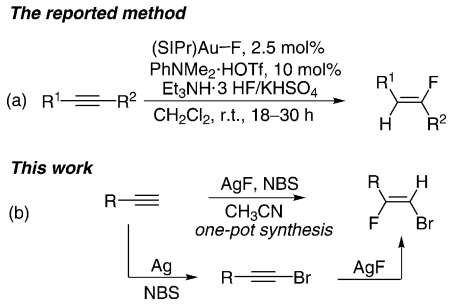
Abstract: The difunctionalization of terminal alkynes was achieved with silver fluoride (AgF) and *N*-bromosuccinimide (NBS) as halogen sources. The presence of the halide moiety greatly enhances the reactivity of the vinyl fluoride compounds that can probably can be transformed into various products that are difficult or even impossible to obtain *via* direct fluorination. Meanwhile, the monofluoro<.>alkenes were facilely synthesized *via* a highly chemo- and regioselective fluorination of electron-deficient C≡C triple bonds using AgF as fluorinating reagent in good yields.

Keywords: bromofluoroalkenes; difunctionalization; fluorination; silver; terminal alkynes

The development of efficient and sustainable methods for the synthesis of halogen-containing olefins is an important task in contemporary catalysis research because of the central role of this class of compounds in biological systems and pharmaceutical applications. Among different protocols for achieving this goal, difunctionalization of C≡C triple bonds to construct C-(sp^2)–X bonds represents a series of reactions with significant synthetic potential.[1,2] Although our ongoing studies on this subject have led to the synthesis of a diverse set of haloalkene derivatives, such as 1-chloro-1,4-dienes,[3a] 1-chlorovinylallenes,[3b] haloalkenynes,[3c] 2-chloro-1,3-dienes,[3d] cyclobutenyl halides[3e] and bromoacrylamides,[3f] it is a challenging issue for us that the fluorine atom can be successfully attached to the resulting olefin by transition metal catalysis. As we know, few effective approaches are available for the direct synthesis of fluoroalkene derivatives without additional functional sites, and transition metal-catalyzed methods are particularly rare.[4] Thus, we sought a mild and expedient protocol to efficiently synthesize difunctionalized fluoroalkenes. The resulting vinyl fluoride compounds should be appealing to synthetic and medicinal chemists due to the unique physical and biological properties imparted by the fluorine atom.[5]

In 2007, Sadighi and co-workers reported that $Et_3N{\cdot}3HF$ could be regarded as fluorine source in Au-catalyzed direct fluorination of C≡C triple bonds [Scheme 1 (a)].[6,7] Inspired by this report, we envisioned the possibility of the synthesis of bromofluoroalkenes from commercially available terminal alkynes in a one-pot manner. Our rationale based on the facts that (i) Ag and Au have similar properties when it comes to catalysis and (ii) bromination of terminal alkynes is feasible under Ag catalysis. This synthetic blueprint should be feasible if the addition of a fluorine source does not interfere with the bromination step.

Highly functionalized *cis*-haloalkenes have been prepared *via* the acetylation and iodation reaction of haloalkynes in a regio- and stereoselective fashion in our group.[8] Herein, we report a general, highly regio- and stereoselective bromofluorination of terminal alkynes by NBS and AgF [Scheme 1 (b)]. Furthermore, we extended this methodology to other internal electron-deficient alkynes and successfully obtained



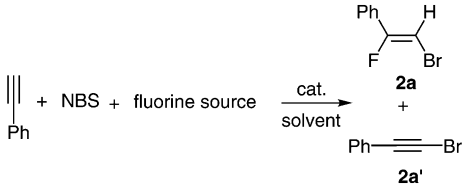
Scheme 1. Reported method for the fluorination and the method presented herein.

the corresponding "HF" cross-addition products. Functionalization of the bromide moiety is also showcased in this report.

Initial investigations focused on validating the bromofluorination of terminal alkynes using various fluorine sources. The reaction of phenylacetylene with NBS was chosen as the starting point (Table 1). When CsF was used as sole fluorine source in the absence of catalysts, only a trace of the desired product was observed (entry 1). Similar results were obtained with various common fluorine sources (KF, TBAF, CuF_2, NiF_2 and *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate) (entries 2–6). We continued to examine the reaction in the presence of Ag or Pd catalysts. Traces of the desired bromofluorination product **2a** were observed under the $CsF/AgNO_3$ reaction system, but phenylethynyl bromide **2a′** was detected as the major by-product (86%) (entry 7). Other catalytic systems, such as pyridinium/$Pd(OAc)_2$, $CuF_2/AgBF_4$ and $NiF_2/AgNO_3$ were ineffective for bromofluorination (entries 8–10). To our delight, when 1.5 equiv. of AgF were employed, the desired bromofluoroalkene **2a** was obtained as major product in 72% yield (entry 11). Further control experiments showed that the use of AgF can significantly improve the yield of **2a** (entry 12). The best result was obtained when the reaction was carried out with 2.5 equiv. of AgF in acetonitrile at 80 °C for 10 h (entry 13). In such a case, the bromofluorination product was formed in 95% yield in an exclusive *cis* fashion, and no phenylethynyl bromide **2a′** was detected. These results indicated that the reaction is mediated by a stoichiometric amount of AgF. A decrease in the temperature lowered the yield of the reaction (entry 14). Compared with the other solvents, acetonitrile is more suitable for the bromofluorination (entries 15 and 16).

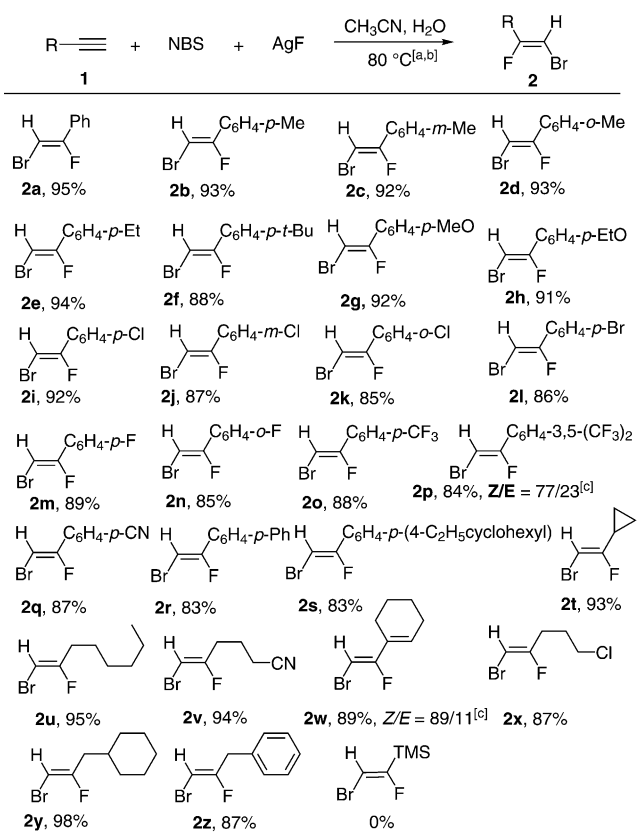
With these optimized reaction conditions in hand, we set out to test the generality of this reaction. Gratifyingly, as shown in Scheme 2, this approach to bromofluoroalkenes is quite versatile. The aromatic al-

Table 1. Optimization of the reaction conditions for phenylacetylene.[a]



Entry	Fluorine source	Additive	Solvent	Yield [%][b] 2a	2a′
1[c]	CsF		CH_3CN	trace	<5
2[c]	KF		CH_3CN	trace	<5
3[c]	TBAF		CH_3CN	trace	<5
4[c]	CuF_2		CH_3CN	trace	<5
5[c]	pyridinium		CH_3CN	trace	<5
6[d]	NiF_2		CH_3CN	<5	15
7	CsF	$AgNO_3$	CH_3CN	<5	86
8	pyridinium	$Pd(OAc)_2$	CH_3CN	<5	<5
9	CuF_2	$AgBF_4$	CH_3CN	<5	83
10	NiF_2	$AgNO_3$	CH_3CN	<5	93
11	AgF		CH_3CN	72	15
12[e]	AgF		CH_3CN	86	8
13[f]	AgF		CH_3CN	95	–
14[g]	AgF		CH_3CN	36	62
15	AgF		THF	55	43
16	AgF		toluene	<5	91

[a] *Reaction conditions:* phenylacetylene (1.0 mmol), NBS (1.1 mmol), fluorine source (1.5 mmol), solvent (2.0 mL) and additive (5 mol%) at 80 °C for 10 h. NBS = *N*-bromosuccinimide, Pyridinium = *N*-fluoro-2,4,6-trimethylpyridinium tetrafluoroborate.
[b] Isolated yield.
[c] Starting material recovered.
[d] 2,2-Dibromo-1-phenylethanone as the major product in 56% yield.
[e] 2.0 mmol AgF.
[f] 2.5 mmol AgF.
[g] Room temperature.



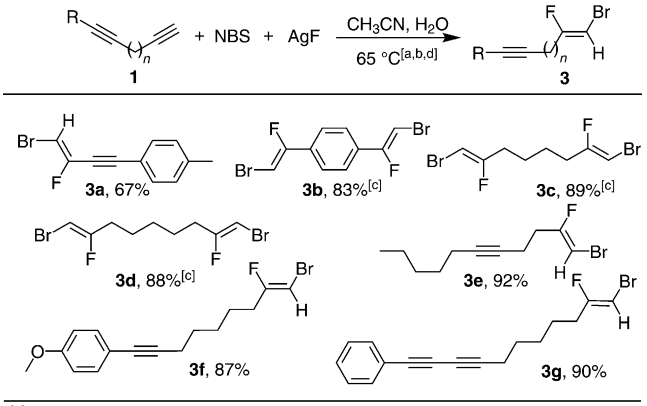
[a] Reaction conditions: terminal alkynes (1.0 mmol), NBS (1.1 mmol), AgF (2.5 mmol), 0.1 mL of H_2O in 2 mL CH_3CN at 80 °C for 10 h.
[b] Isolated yields are given.
[c] The Z/E ratio was determined by GC or NMR. Unless otherwise noted, *Z/E* ratio > 95:5.

Scheme 2. Synthesis of bromofluoroalkenes with various terminal alkynes.

kynes with either electron-donating or electron-withdrawing groups attached to the benzene rings, were able to undergo bromofluorination smoothly and generated the corresponding products in good to excellent yields (Scheme 2, **2a–2s**). The reaction of alkynes containing electron-rich groups provided slightly higher yields than those conatining electron-poor groups. The reaction tolerated a variety of substituents including Cl, Br, F, CN, CF_3, NO_2 and OMe groups. Substituents at the *ortho* position of the benzyl group did not affect the yield of the reaction (Scheme 2, **2d** and **2n**). The steric hindrance of the 3,5-bis(trifluoromethyl)benzene ring has a negligible effect on the yield in spite of the lowered stereoselectivity (Z:E = 77:23, Scheme 2, **2p**). Besides the arylalkynes, aliphatic alkynes were also found to be suitable substrates for the standard conditions. When ethynylcyclopropane was employed, the desired bromofluoroalkene was formed in excellent isolated yield (Scheme 2, **2t**). Cyanide-containing aliphatic alkynes has also been successfully employed without protection, and the chemistry provides the desired bromofluoroalkenes in good yields (Scheme 2, **2v**). Herein, simple filtration through a silica-gel plug was sufficient to remove the residual catalyst and provide desired products. It is noteworthy that 1-ethynylcyclohex-1-ene works effectively, and that *gem*-difluoroalkanes are not observed in our process despite the fact that *gem*-difluoroalkanes have been reported as the major products by addition of "XF" to alkenes (Scheme 2, **2w**).[9] Unfortunately, the reaction with ethynyltrimethylsilane only afforded fluorotrimethylsilane as the product.

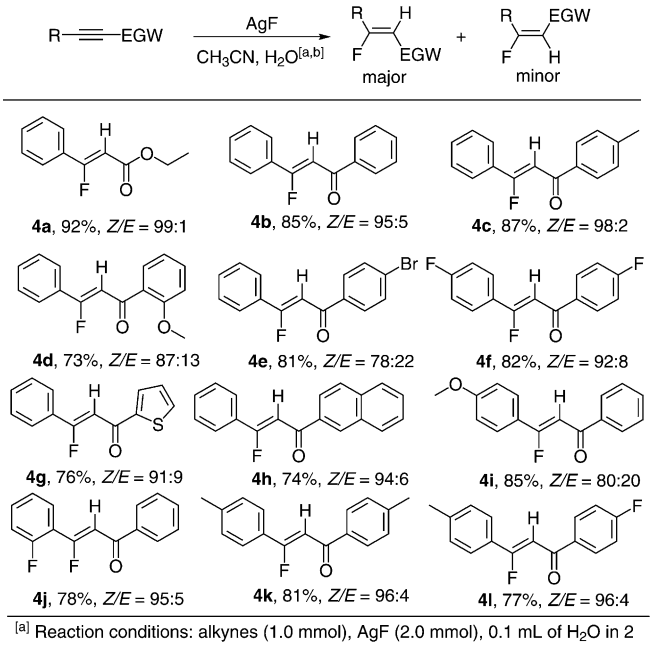
The bromofluorination of the 1,n-diyne system is equally interesting. The major challenge in this reaction is the control of chemo- and regioselectivity, since examples of chemo- and regioselective fluorination involving alkynes are still limited.[10] It is observed that an electron-rich internal C≡C triple bond was tolerated under the present conditions. Thus, 1-(buta-1,3-diynyl)-4-methylbenzene reacts with NBS and AgF to generate the corresponding bromofluoroalkene in moderate yield with the internal alkyne intact (**3a**). Moreover, similar results were observed for other diyne or triyne compounds (**3e**, **3f** and **3g**) with only the terminal triple bond being bromofluorinated (Scheme 3). On the other hand, bromofluorination occurred readily on both of the terminal C≡C triple bonds when such substrates were used (**3b**, **3c** and **3d**). The molecular structure of compound **3b** was established by X-ray crystallography, which enabled us to confirm the reaction mechanism as a *cis*-addition process (see the Supporting Information).[11]

The above studies dealt only with terminal alkynes as the reactive point in the substrates. For extensions, we used other electron-deficient compounds, such as substituted aryl alkynyl ketones, to investigate the potential of this transformation (Scheme 4). Similar to ethyl 3-phenylpropiolate, phenyl alkynyl ketone was able to afford the corresponding fluorination products in good yields. It was found that structurally various phenyl alkynyl ketone showed high reactivities with AgF, affording the products in high Z/E selectivities.[12,13] In addition, a heterocyclic compound, 3-phenyl-1-(thiophen-2-yl)prop-2-yn-1-one, was equally amenable to the applied reaction conditions and



[a] *Reaction conditions:* terminal alkynes (1.0 mmol), NBS (1.1 mmol), AgF (2.5 mmol), CH_3CN (2 mL) at 65 °C for 10 h.
[b] Isolated yields are given.
[c] NBS (2.2 equiv.) and AgF (5.0 equiv.).
[d] The *Z*/*E* ratio was determined by GC or NMR. Unless otherwise noted, *Z*/*E* ratio > 95:5.

Scheme 3. Synthesis of bromofluoroalkenes with various diynes.



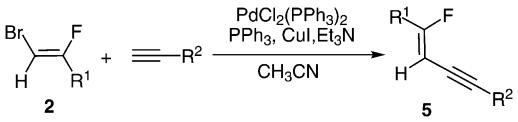
[a] Reaction conditions: alkynes (1.0 mmol), AgF (2.0 mmol), 0.1 mL of H_2O in 2 mL CH_3CN at 80 °C for 10 h.
[b] Isolated yields are given.
[c] The *Z*/*E* ratio was determined by GC analysis of the crude product.

Scheme 4. Synthesis of monofluoroalkenes with various electron-deficient alkynes.

formed the hydrofluorination product **4g** in good yield.

The obtained bromofluoroalkenes are highly attractive as intermediates for the preparation of more functionalized fluoroalkenes. The synthetic versatility of the bromofluorination products is demonstrated by the transformations shown in Table 2. Under these reaction conditions, various 1-fluoro-1,3-enynes could be stereoselectively prepared from bromofluoroalkenes and terminal alkynes, which are difficult to obtain *via* direct fluorination of the 1,3-diyne. To demonstrate the synthetic utility of bromofluoroalkenes, we showed that the Pd/Cu-catalyzed coupling of bromofluoroalkenes with terminal alkynes gave 1-fluoro-1,3-enyne products in good yields. Since 1-fluoro-1,3-enyne products are found in materials science and biologically active products, the presented synthetic scheme should be applicable to access this class of compounds, starting with readily available terminal alkynes.[14] It is noteworthy to point out that **2f** also reacted with phenylboronic acid to give 1-((*Z*)-1-fluoro-2-phenylvinyl)-4-methoxybenzene in 91% yield (Scheme 5).

Table 2. Transformations of bromofluoroalkenes.[a]



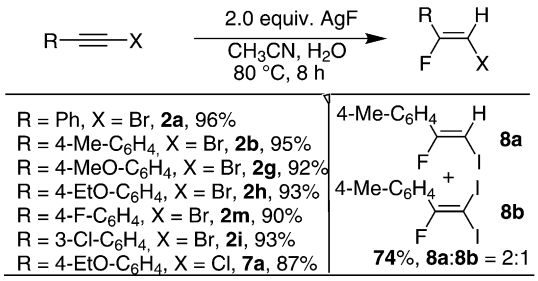
2 **5**

Entry	Bromofluoro-alkene: R^1	Alkyne R^2	Prod-uct	Yield [%][b]
1	**2a**: Ph	TMS	**5a**	92
2	**2b**: 4-Me-C_6H_4	TMS	**5b**	91
3	**2c**: 3-Me-C_6H_4	TMS	**5c**	88
4	**2d**: 2-Me-C_6H_4	TMS	**5d**	86
5	**2e**: 4-Et-C_6H_4	TMS	**5e**	93
6	**2g**: 4-MeO-C_6H_4	TMS	**5f**	85
7	**2i**: 4-Cl-C_6H_4	TMS	**5g**	84
8	**2m**: 4-F-C_6H_4	TMS	**5h**	86
9	**2o**: 4-CF_3-C_6H_4	TMS	**5i**	87
10	**2b**: 4-Me-C_6H_4	4-Cl-C_6H_4	**5j**	88

[a] *Reaction conditions:* bromofluooalkenes (1.0 mmol), terminal alkynes (1.6 mmol), $PdCl_2(PPh_3)_2$ (5 mol%), CuI (10 mol%), Et_3N (3.0 mol), Ph_3P(10 mol%) in 2 mL CH_3CN at 70 °C for 10 h.

[b] Isolated yields are given.

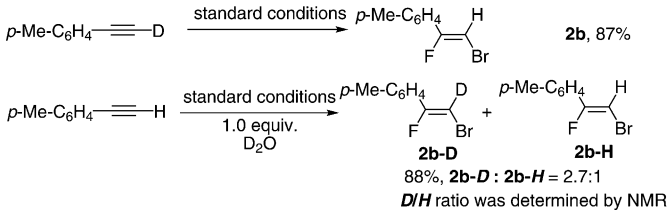
To obtain further insight into the mechanism of the present catalytic process, the direct fluorination of haloalkynes were performed, as shown in Scheme 6.



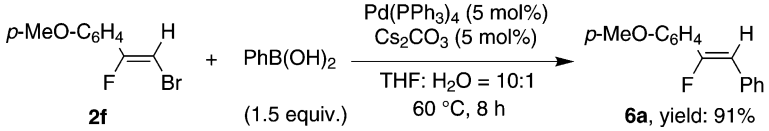
Scheme 6. The direct fluorination of haloalkynes.

Gratifyingly, both bromoalkyne and chloroalkyne exclusively gave the fluorination products in good yields (Scheme 6, **2a**–**7a**). In addition, the iodofluoroalkene (**8a**) was found to be obtained in a 2:1 ratio with 1-(1-fluoro-2,2-diiodovinyl)-4-methylbenzene (**8b**), suggesting that iodoalkynes may be more active in comparison with bromoalkynes and chloroalkynes.

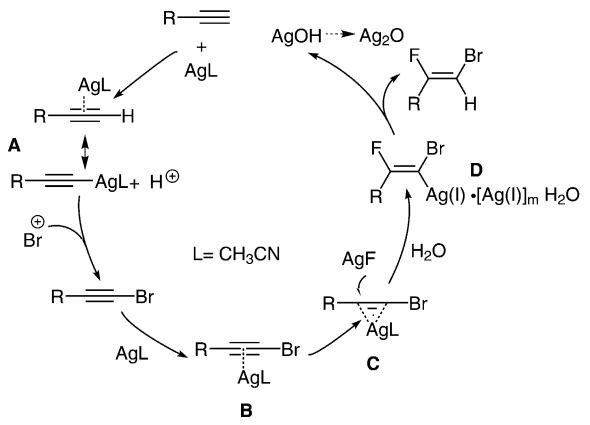
Next, two experiments were carried out to identify the source of hydrogen in the products (Scheme 7). When 1-ethynyl-4-methylbenzene with the alkynyl proton deuterated was used as a substrate only **2b** was obtained in 87% isolated yield. Moreover, under the optimized condition, 1.0 equiv, D_2O instead of H_2O was added and a successful bromofluorination afforded the mixture **2b-*D*** and **2b-*H*** in 88% yield with a 2.7:1 ratio. These results provided evidence that this chemistry presumably proceeds through the haloalkyne intermediates, which can be readily prepared from the bromination of terminal alkynes in the the presence of Ag catalysis.[15] As we know, cationic silver species have been regarded as effective catalysts for electrophilic activation of alkynes toward



Scheme 7. Control experiments.



Scheme 5. Transformations of bromofluroralkene.



Scheme 8. Tentative mechanism for the bromofluorination reaction.

a variety of nucleophiles.[16] Consequently, possible mechanisms were proposed based on the previous literature and our experimental results (Scheme 8).[6,7,17] First, the bromoalkyne is formed by Ag-catalyzed bromination of terminal alkynes. Then, the silver cation is attacked by the triple bond of bromoalkyne to form a π-complex **B**, which is then converted to the corresponding vinyl-sliver intermediate **D** by *trans*-addition of AgF to bromoalkyne. Protonation of the vinyl-sliver intermediate **D** gives (*Z*)-2-bromo-1-fluoroalkene as the product and silver oxide.[18] The high regio- and stereoselectivity of the product originates from the back-side attack of fluoride (**C** to **D**).[8d] The bromide atom is regarded as both an activating and regio-directing group. Another mechanism including nucleophilic addition of fluorine anion to bromoalkyne form vinyl-sliver intermediate **D** also cannot be ruled out.[8]

In conclusion, a new route to bromofluoroalkenes was developed *via* the silver-assisteded difunctionalization of terminal alkynes with NBS and AgF. The presented bromofluorination reaction has several advantages, such as ready availability of all reagents, substrates with broad functional group tolerance, extremely mild reaction condition, one-pot synthesis with excellent selectivity and excellent yields. The obtained bromofluoroalkenes can serve as direct precursors for biologically active compounds and advanced materials. Current efforts aimed at further elucidating the detailed reaction mechanism and applying the bromofluorination process for synthesis of complex fluorine-containing olefin are underway.

Experimental Section

General Procedure

Terminal alkyne (1.0 mmol), NBS (1.1 mmol) and AgF (2.5 mmol), 0.1 mL of H_2O in 2 mL CH_3CN were added to a sealed tube. The reaction mixture was stirred at 80 °C for 10 h. After completion of the reaction, the solution was diluted with ethyl acetate, washed with water and brine. The organic layer was then dried over anhydrous Na_2SO_4 and the solvent was removed under vacuum. The residue was finally purified by column chromatography on silica gel using petroleum ether-ethyl acetate mixture as eluent.

Acknowledgements

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[11] The cif file for the compound **3b** has been deposited in Cambridge Crystallographic Data Center. CCDC 806256 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif or from the Director, CCDC, 12 Union Road, Cambridge CB2 1EZ, UK, (Fax: +44-1223-336-033; Email: deposit@ccdc.cam.ac.uk).

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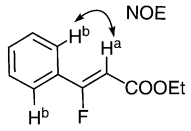

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