ORGANIC CHEMISTRY

Stereoselective synthesis of geminal bromofluoroalkenes by kinetically controlled selective conversion of oxaphosphetane intermediates

Jaeseong Jin[1], Su-min Song[1,2], Jun-Ho Choi[1]*, Won-jin Chung[1]*

Geminal bromofluoroalkenes are an important subclass of versatile organic interhalide, which can serve as useful synthetic precursors to monofluoroalkenes that are valuable amide group isosteres. Nonetheless, despite the vast advancement of olefination methodologies, the broadly applicable stereoselective synthesis remained elusive for geminal bromofluoroalkenes before our work. In particular, the seemingly straightforward Wittig-type approach with interhalogenated phosphorus ylide has been unsuccessful because of the difficulty in the diastereoselective oxaphosphetane formation. Here, we describe a conceptually distinctive strategy, by which the stereoselectivity is gained via the selective decomposition of the oxaphosphetane intermediates. The suitably identified phosphorus(III) reagent and reaction medium enabled efficient kinetic differentiation, which was supported by nuclear magnetic resonance analysis and density functional theory calculation. Through our method, the highly diastereoselective synthesis of geminal *E*-bromofluoroalkenes was accomplished in one step. Furthermore, the generality was demonstrated by accommodating a wide range of readily available carbonyl compounds, including ketones and pharmaceutical substrates.

INTRODUCTION

Geminal dihaloalkenes are versatile synthetic intermediates for highly functionalized alkenes and a variety of transformations in organic chemistry (*1*–*4*). Moreover, these structural motifs are found in bioactive molecules (*5*–*8*). Among numerous synthetic methods (*2*, *3*), the preparation of geminal dihaloalkenes has been commonly accomplished via the Wittig-type carbonyl olefination by using a polyhalomethane and PPh_3. This approach is convenient and highly useful in accessing homo-dihaloalkenyl moieties, which do not involve stereochemical issues. On the other hand, the construction of related structures with two different halogens suffers from low diastereoselectivity (Fig. 1A) (*2*, *9*). Although other procedures have been developed for the synthesis of geminally interhalogenated olefins in a diastereoenriched form, including halofunctionalization of haloalkynes (*10*–*12*), sequential halogenolysis of geminal heterobimetallic alkenes (*13*), halodestannylation of geminal fluorostannylalkenes (*14*), lithiation/halogenation of geminal dibromoalkenes (*15*), reductive elimination of dibromofluoroethyl alcohols (*16*), and Cu-catalyzed geminal bromofluoroolefination of hydrazones (*17*), these reactions have critical drawbacks such as inefficient multi-step process, narrow substrate scope, and/or harsh reaction conditions. Consequently, there has still been no general and practical route for stereoselective geminal interhaloolefination, although the large reactivity difference between two halogens in the products provides high synthetic utility for the stereospecific synthesis of multifuntionalized alkenes (*2*).

Geminal bromofluoroalkenes (**1**) can serve as useful synthetic precursors to monofluoroalkenes (*2*, *18*–*22*), which have been used as an amide group isostere to improve biological properties (Fig. 1B) (*23*–*26*). Therefore, the selective synthesis of **1** in a diastereoenriched form is of high importance because only one stereoisomeric form of monofluoroalkene moieties can mimic the steric and electronic properties of the target amide bond (*27*–*30*). Nonetheless, **1** has been generally prepared via the unselective Wittig-type dihaloolefination using P(III) reagents and $CFBr_3$ (Fig. 1C) (*9*, *31*–*33*). Moreover, the necessity of harmful additives such as Et_2Zn or the generation of toxic $O{=}P(NMe_2)_3$ byproduct diminishes the practicality of this process. Although it is possible to enrich one stereoisomer from the mixture via base-promoted chemoselective consumption of *Z*-alkene (*31*) or Pd-catalyzed debromination of *E*-alkene (*34*), the requirement of an additional manipulation step and the consequent attenuation of functional group compatibility decreased the synthetic utility. Thus, it is highly desirable to develop an efficient and broadly applicable strategy for the stereoselective construction of **1**.

Although the reaction conditions using a P(III) reagent with $CFBr_3$ have been continuously used for the synthesis of **1**, the P(III) scope has been largely limited to PPh_3 and $P(NMe_2)_3$ (*35*–*40*). Thus, we set out our investigation by surveying structurally and electronically diverse P(III) compounds to unveil their role in geminal bromofluoroolefination. Then, while examining phosphonites, we observed an unprecedentedly high level of diastereocontrol. Whereas the stereoselectivity of Wittig-type reactions is typically determined during the formation of oxaphosphetane via a formal [2 + 2] cycloaddition between aldehyde and phosphorus ylide (*41*, *42*), which has not been successful for interhalide cases, our reaction appeared to proceed through a previously undiscovered stereocontrolling strategy, in which highly selective formation of **1** was achieved during the oxaphosphetane decomposition step (Fig. 1D). Here, we report a general synthetic approach toward geminal *E*-bromofluoroalkenes through kinetically selective conversion of *trans*-**3** by using a suitably identified P(III) reagent, $PhP(O\textit{i}\text{-}Pr)_2$, under nonpolar reaction conditions (Fig. 1E). Our newly developed strategy can accommodate a wide range of carbonyl substrates, including ketones and pharmaceutically relevant compounds, in one step with excellent *E*-selectivity under mild reaction conditions. Furthermore, the quantitative ^{19}F nuclear magnetic resonance (NMR) analysis of the reaction progress confirmed the substantial reactivity difference

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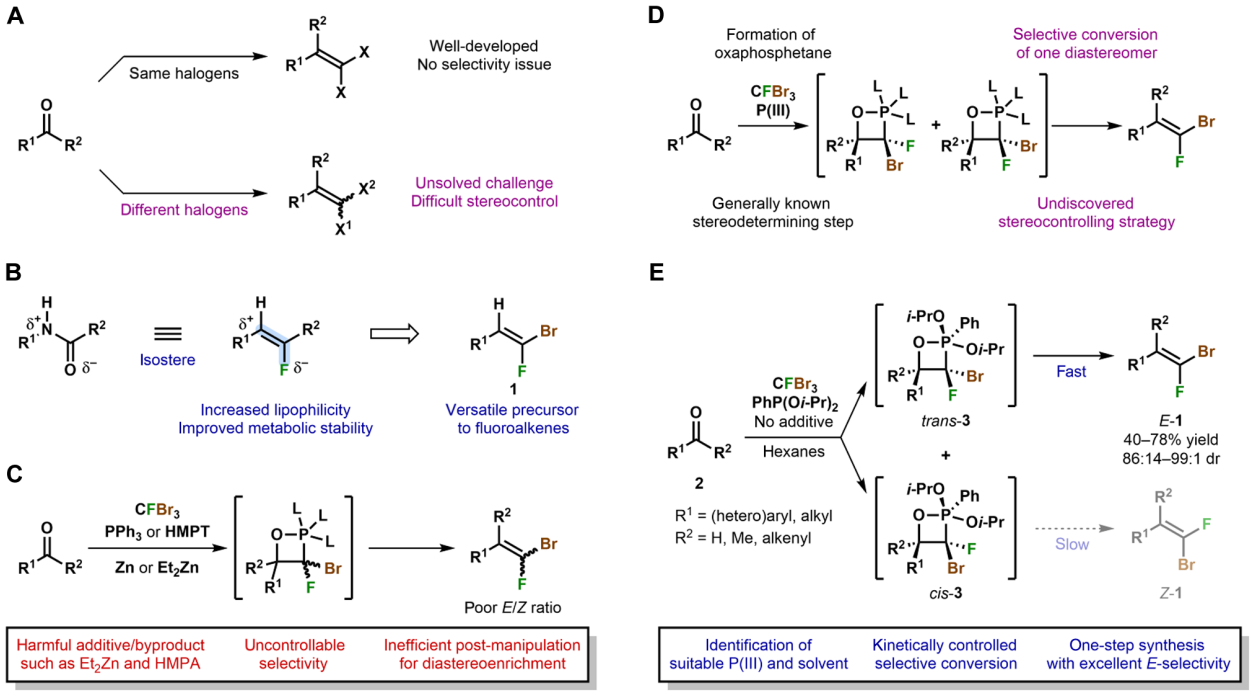


Fig. 1. Research outline. (**A**) Difficulty in diastereoselective synthesis of geminally interhalogenated alkenes. (**B**) Geminal bromofluoroalkenes as versatile precursors to monofluoroalkenes, an isostere of amide. (**C**) Drawbacks of previous geminal bromofluoroolefination. (**D**) Undiscovered stereocontrolling strategy through selective conversion of one oxaphosphetane diastereomer. (**E**) This work: kinetically controlled, highly *E*-selective geminal bromofluoroolefination via PhP(O*i*-Pr)$_2$–mediated, faster transformation of *trans*-oxaphosphetane.

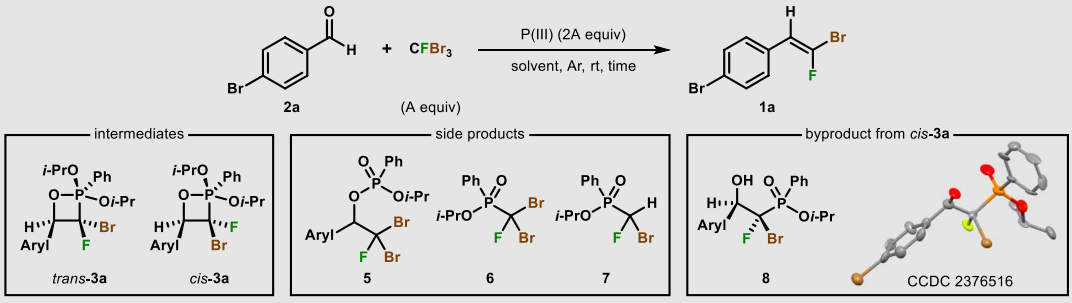
between *trans*-**3** and *cis*-**3**, the origin of which was then elucidated by computational analysis.

RESULTS

Reaction condition optimization

The reaction conditions for the geminal bromofluoroolefination were optimized with 4-bromobenzaldehyde (**2a**) (Table 1). At the outset, the reaction was performed with PPh_3 in CH_2Cl_2 at room temperature, but the stereoselectivity was negligible (entry 1). In the presence of P(O*i*-Pr)$_3$, which had been used for the synthesis of geminal bromofluoroalkenes (*38*) and dibromoalkenes (*43*) via the Wittig-type olefination, the product **1a** was obtained in an improved 65% NMR yield. However, the lack of stereoselectivity was unresolved (entry 2). Both yield and *E*-selectivity were increased when one O*i*-Pr was replaced with Ph (entry 3). An even higher yield was afforded with Ph_2PO*i*-Pr, but the *E*/*Z* selectivity was decreased (entry 4). The analysis of the crude mixture from the reaction in entry 3 indicated the formation of several side products **5** to **7**, which were presumed to be formed via nucleophilic dealkylation of phosphorus alkoxide intermediates. Thus, nonpolar solvents were briefly surveyed to attenuate those S_N2 side reactions. Remarkably, **1a** was produced with excellent 93:7 *E*-selectivity in 61% NMR yield when the reaction was conducted in hexanes (entry 5). Although the generation of the side products was not completely suppressed, **1a** could be isolated easily in a pure form by simple silica gel filtration with hexanes. Rate acceleration was observed when toluene was used as another nonpolar solvent, but slightly lower stereoselectivity was obtained (entry 6). On the other hand, the examination of cyclohexane resulted in a diminished yield, albeit with an improved *E*/*Z* selectivity (entry 7). Thus, further optimization was conducted in hexanes. There were no meaningful changes by increasing the amounts of $CFBr_3$ and PhP(O*i*-Pr)$_2$ (entry 8). On the contrary, the reaction with lower loadings of reagents led to a drastically decreased yield because of incomplete consumption of aldehyde (entry 9). During the optimization of the reaction conditions, it was noticed that the reaction outcome was highly influenced by the reaction time. When the reaction was halted after 1 hour, the highest 98:2 *E*-selectivity was obtained despite the poor yield (entry 10). In contrast, the stereoselectivity was slightly eroded after 6 hours (entry 11). On the basis of these experimental data, it was hypothesized that the faster transformation of *trans*-**3a** compared to *cis*-**3a** could give rise to higher stereoselectivity at an early stage of the reaction, whereas longer reaction time would only cause continuing decomposition of *cis*-**3a** to *Z*-**1a** even after the full conversion of *trans*-**3a**, resulting in diminished *E*-selectivity. Hence, the reaction progress was quantitatively analyzed by ^{19}F NMR spectroscopy to determine the optimal reaction time (Fig. 2). Within 1 hour, **2a** was completely converted to a diastereomeric mixture of **3a**. As expected, a substantially faster reaction of *trans*-**3a** to *E*-**1a** was observed, affording a high level of diastereoselectivity. Most of *trans*-**3a** was transformed after 4 hours, and further reaction only eroded the *E*/*Z* ratio (for details, see figs. S7 and S8 and table S1). This experimental observation revealed the superior reactivity of *trans*-**3a** over *cis*-**3a**. It appeared that the use of PhP(O*i*-Pr)$_2$ as well as hexanes enhanced the difference in reactivity between the oxaphosphetane diastereomers, thereby enabling unprecedentedly high *E*-selectivity. For a further improvement of the stereoselectivity, the reaction was carried

Table 1. Reaction condition optimization. Reaction conditions: **2a** (0.2 mmol), $CFBr_3$ (A equiv), and P(III) (2A equiv) in solvent (1.0 ml). NA, not applicable.



Entry	P(III)	Solvent	Time (hours)	A	Yield (%)*	*E*:*Z*†
1	PPh_3	CH_2Cl_2	2	2.0	54	57:43
2	$P(Oi\text{-}Pr)_3$	CH_2Cl_2	2	2.0	65	55:45
3	$PhP(Oi\text{-}Pr)_2$	CH_2Cl_2	2	2.0	83	64:36
4	$Ph_2POi\text{-}Pr$	CH_2Cl_2	2	2.0	91	50:50
5	$PhP(Oi\text{-}Pr)_2$	Hexanes	4	2.0	61 (55)‡	93:7 (95:5)‡
6	$PhP(Oi\text{-}Pr)_2$	Toluene	1	2.0	62 (57)‡	93:7 (93:7)‡
7	$PhP(Oi\text{-}Pr)_2$	Cyclohexane	4	2.0	50	96:4
8	$PhP(Oi\text{-}Pr)_2$	Hexanes	4	2.5	63	91:9
9	$PhP(Oi\text{-}Pr)_2$	Hexanes	4	1.5	36	97:3
10	$PhP(Oi\text{-}Pr)_2$	Hexanes	1	2.0	17	98:2
11	$PhP(Oi\text{-}Pr)_2$	Hexanes	6	2.0	62	92:8
12§	$PhP(Oi\text{-}Pr)_2$	Hexanes	12	2.0	10	97:3
13	$PhP(OMe)_2$	Hexanes	4	2.0	0	NA
14	$PhP(OCy)_2$	Hexanes	4	2.0	0	NA
15	$PhP(Ot\text{-}Bu)_2$	Hexanes	4	2.0	0	NA
16	$PhP(OCH_2t\text{-}Bu)_2$	Hexanes	4	2.0	13	71:29

*Yields based on ^{19}F NMR analysis with 2-fluorobiphenyl (0.2 mmol) as an internal standard. †Determined by ^{19}F NMR analysis. ‡Data of the isolated materials from the reactions on a 1.0 mmol scale in parentheses. §At 0°C.

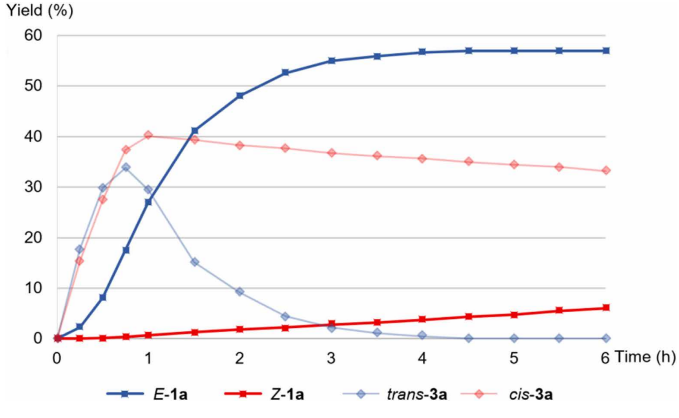


Fig. 2. ^{19}F NMR monitoring of the reaction progress.

out at 0°C to minimize the conversion of *cis*-**3a** (entry 12). However, the reaction was slowed down dramatically, giving **1a** only in 10% yield. Last, additional fine-tuning was performed through examination of various phosphonites with modulated steric properties. Unfortunately, the use of small alkyl-substituted phosphonite, $PhP(OMe)_2$, was detrimental as the phosphinate side products analogous to **6** and **7** were formed via the facile Michaelis-Arbuzov–type demethylation of the phosphorus ylide (entry 13). To prevent these S_N2 side reactions, phosphonites with bulkier cyclohexyl, *tert*-butyl, and neopentyl groups were examined (entries 14 to 16). However, a complex mixture containing phosphinates was obtained using $PhP(OCy)_2$ (entry 14). Also, the desired product **1a** was not generated at all from the reaction with $PhP(Ot\text{-}Bu)_2$ probably because the *tert*-butyl group interferes with the formation of ylide (entry 15). Similarly, the low reactivity of $PhP(OCH_2t\text{-}Bu)_2$ toward $CFBr_3$ resulted in a substantially attenuated yield of **1a** (entry 16). The optimal reactions in entries 5 and 6 were reproducible on a preparative (1 mmol) scale. Furthermore, byproducts **8** were produced from the unreacted *cis*-**3a** upon silica gel filtration as a mixture of diastereomers at phosphorus. The structure of an isomer of **8** was unambiguously determined by single-crystal x-ray diffraction analysis, confirming the relative configuration of the two adjacent carbon centers (see fig. S11).

Substrate scope

Under the optimal reaction conditions, substrate scope was explored with a wide range of carbonyl compounds (Fig. 3). The appropriate reaction time for each substrate was estimated by ^{19}F NMR analysis of the reaction progress (for representative examples,

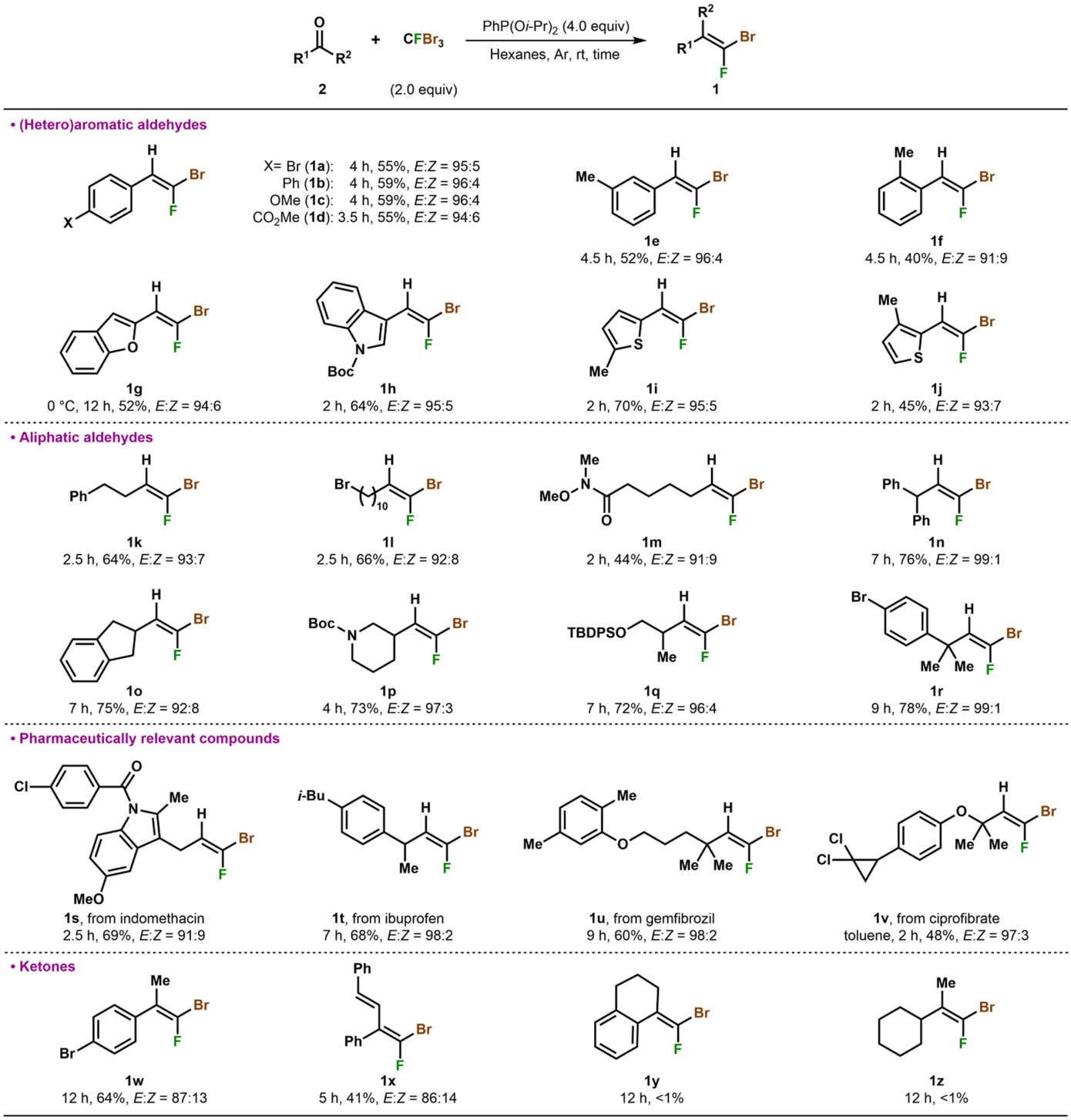


Fig. 3. Substrate scope of PhP(O*i*-Pr)$_2$–mediated stereoselective synthesis of geminal bromofluoroalkenes. Reaction conditions: **2** (1.0 mmol), $CFBr_3$ (2.0 mmol), and PhP(O*i*-Pr)$_2$ (4.0 mmol) in hexanes (except **1v**) (5 ml for aldehydes and 2 ml for ketones) at room temperature (rt) (except **1g**). Isolated yields after silica gel filtration are given.

see figs. S1 to S6). Consistently high reactivity was observed regardless of the electronic property of the aromatic aldehydes. The geminal bromofluoroalkenes with *p*-Ph, OMe, or CO_2Me groups (**1b** to **1d**) were obtained in good yields with excellent stereoselectivity. In addition, our reaction tolerated substituents at any position on the aryl rings. From *m*-tolualdehyde (**2e**), the corresponding product **1e** was afforded in 52% yield with 96:4 *E*/*Z* ratio. The presence of sterically hindering *o*-methyl group (**2f**) was allowed to give **1f** with 91:9 *E*-selectivity, albeit in a slightly diminished yield because the *trans*-intermediate (*trans*-**3f**) was generated in a smaller portion compared to other aromatic aldehydes. When heteroaryl aldehydes (**2g** to **2j**) were used, relatively faster conversion of *cis*-**3** was observed

at room temperature by ^{19}F NMR analysis, resulting in attenuated stereoselectivity. Thus, the reaction temperature was lowered to 0°C, or the reaction time was shortened. By these modifications, the geminal bromofluoroalkene with 2-benzofuranyl group (**1g**) was formed in 52% yield with 94:6 *E*/*Z* selectivity at 0°C, and **1h** containing *N*-Boc-3-indolyl group was afforded in 64% yield with 95:5 *E*-selectivity in 2 hours. Likewise, the products with a thienyl group (**1i** and **1j**) were isolated with excellent stereoselectivity. The relatively low yield of **1j** was probably caused by steric encumbrance, similarly to the result from **2f**. Further examination was conducted with a variety of aliphatic aldehydes. Primary alkyl aldehyde **2k** smoothly underwent geminal bromofluoroolefination to produce **1k** in 64% yield with 93:7 *E*-selectivity. In addition, it was possible to obtain **1l** containing a sensitive primary alkyl bromide moiety in 66% yield with 92:8 *E*-selectivity. This result is noticeable because an unselective formation of *E*/*Z* isomers from **2l** was observed previously in only 18% yield under the PPh_3/Et_2Zn conditions (*22*). Also, an aldehyde containing the synthetically versatile Weinreb amide (**2m**) was successfully used to give **1m** in 44% yield with high stereoselectivity. Bulkier aliphatic aldehydes were even better substrates. From secondary aldehyde **2n**, the product **1n** was afforded in 76% yield with essentially exclusive *E*-selectivity. Again, our one-step process is superior to the previous two-step preparation of *E*-**1n** that required the inefficient base-promoted consumption of *Z*-isomer (*22*). Moreover, the geminal bromofluoroalkene with a 2-indanyl group (**1o**) was isolated in 75% yield with a high *E*/*Z* ratio. The aldehydes with a Boc-protected amine or a silyl ether (**2p** and **2q**) were well tolerated to give **1p** and **1q** with exquisite stereocontrol in 73% and 72% yields, respectively. Remarkably, even in the case of tertiary aliphatic aldehyde **2r**, **1r** was furnished in 78% yield with exceptional 99:1 *E*-selectivity, implying much more favorable formation and superior reactivity of *trans*-oxaphosphetane. Furthermore, it is worth noting that our newly developed method was applicable to pharmaceutically relevant compounds, providing **1s** to **1v** in 48 to 69% yields with 91:9 to 98:2 diastereoselectivity. In an attempt to expand the substrate scope even further, a few ketones were evaluated. Gratifyingly, geminal bromofluoroolefination of an acetophenone derivative **2w** was successfully conducted to produce **1w** in 64% yield with an unprecedented level of 87:13 *E*/*Z* selectivity for ketone. Moreover, the product with an alkenyl substituent **1x** was compatible, resulting in a 41% yield with 86:14 *E*-selectivity from *trans*-chalcone (**2x**). In the cases of 1-tetralone (**2y**) and cyclohexyl methyl ketone (**2z**), only trace amounts of **1y** and **1z** were obtained probably because the phosphorus ylide was not sufficiently reactive toward more sterically hindered and/or less electrophilic ketones.

Computational analysis

To gain insight into the excellent diastereoselectivity arising from the superior reactivity of *trans*-**3** compared to *cis*-**3**, density functional theory (DFT) calculation was conducted at the ωB97X-D/def2TZVP/IEFPCM(*n*-hexane) level of theory (Fig. 4A) (*44*–*48*). The geminal bromofluoroolefination is initiated by complexation between aldehyde and phosphorus ylide (**INT I**) (*49*). Subsequently, oxaphosphetane **3** (**INT II**) is generated by a formal [2 + 2] cycloaddition via **TS I**. This process is highly exothermic, and the small activation energy is consistent with the fast formation of **3** at room temperature. Also, the 0.5 kcal/mol lower barrier for *trans*-**3** accounts for its slightly dominant production as observed by quantitative ^{19}F NMR analysis (Fig. 2). The calculated structure of *trans*-**3** is 0.4 kcal/mol more stable than that of *cis*-**3**, but the following **TS II** from *trans*-**3** has a 2.5 kcal/mol lower energy probably because of the evolving partial alkene structure that resembles the more stable *E*-isomer. As a result, in the rate-determining step, the conversion of *trans*-**3** is more favorable by 2.1 kcal/mol, allowing the kinetically controlled *E*-selectivity.

The origin of this phenomenon is interpreted by inspection of the optimized structures of the conformationally distinct, diastereomeric oxaphosphetane intermediates **3** (Fig. 4B). It appears that a strong hyperconjugative interaction is present in *cis*-**3** (blue arrow) as evidenced by the nearly *anti*-periplanar orientation between the C^3—P and the C^2—Br bonds ($\angle C^3PC^2Br = 172°$). This proposition is also supported by the elongation of the C^2—Br bond (1.95 Å) compared to that in *trans*-**3** (1.94 Å). It is presumed that the strong electron-accepting ability of $\sigma^*(C^2—Br)$ enabled such an interaction with $\sigma(C^3—P)$ in *cis*-**3** (*50*). In consequence, the C^2—P bond contracts (1.88 Å versus 1.93 Å) and the O^1PO^3 angle becomes wider (161° versus 144°), which places two electronegative oxygen atoms, O^1 and O^3, into the pseudo-apical positions, permitting a hypervalent three-center four-electron $O^1—P—O^3$ bonding with stretched O—P bonds (1.74 and 1.63 Å versus 1.69 and 1.61 Å) (*51*). Therefore, *trans*-**3** has both the relatively longer C^2—P bond and the shorter O^1—P bond, which should be advantageous for the subsequent phosphonate dissociation (*52*).

Furthermore, the beneficial solvent effect of hexanes is rationalized. In both diastereomers of **3**, the two bulky phenyl groups are located on the opposite side of the small four-membered ring to avoid steric encumbrance, and then the positions of the two alkoxy substituents around the phosphorus center are restricted. As a result, the strong dipole moments of the highly polarized C^2—F and O^2—P bonds in *cis*-**3** (purple arrows) cancel out, leading to the minimized overall dipole moment. Therefore, the reactive, more polar isomer *trans*-**3** would be relatively destabilized and thus further activated in nonpolar solvents. This argument is supported by an additional calculation using the CH_2Cl_2 solvation (see fig. S10), which shows a much smaller activation energy difference (1.2 kcal/mol). In addition, the lower activation barriers (≤26 kcal/mol) would make both diastereomeric pathways too fast to be kinetically distinguishable. These computational results are in good agreement with the experimental observation of a substantially improved *E*/*Z* ratio in hexanes compared to in CH_2Cl_2 (Table 1, entry 3 versus entry 5).

Finally, synthetic utility of geminal bromofluoroalkene was demonstrated by performing a stereospecific transformation of the more reactive bromine substituent, and the Sonogashira coupling of **1k** with (trimethylsilyl)acetylene afforded 2-fluoro-1,3-enyne **9** in 86% yield without erosion of the stereochemical integrity (Fig. 5A). Notably, our process is complementary and also superior to the previous Julia olefination method, which gave the opposite alkene configuration with moderate selectivity (Fig. 5B) (*53*).

DISCUSSION

In summary, we have discovered an unprecedented stereocontrolling strategy for the Wittig-type interhaloolefination by taking advantage of the reactivity difference between the diastereomeric oxaphosphetane intermediates. The identification of a suitable P(III) reagent and a solvent that maximize the kinetic difference is the key factor for the successful accomplishment. Through this method, synthetically

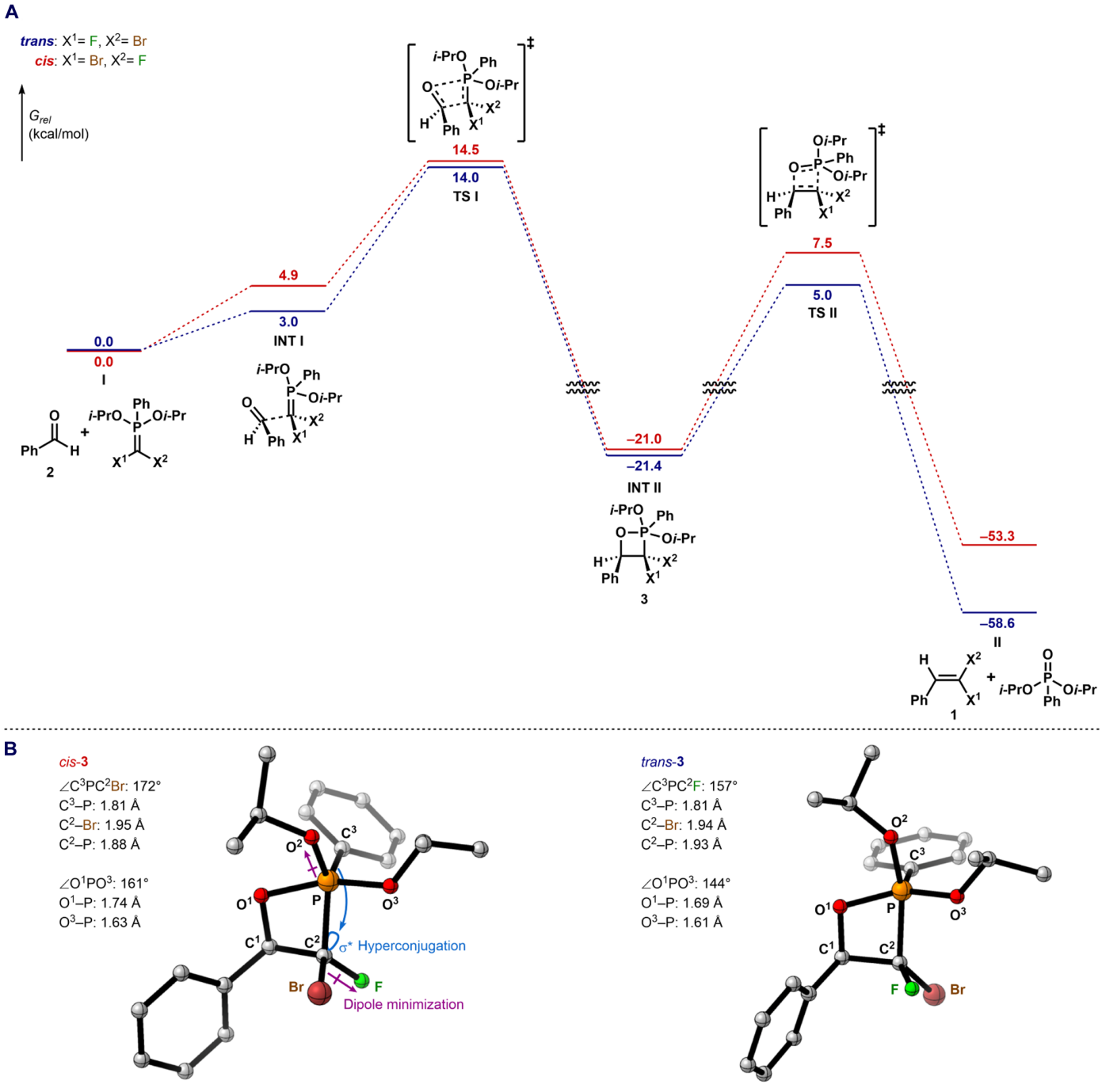


Fig. 4. Computational analysis on the reaction mechanism. (**A**) Gibbs free energy profile at the ωB97X-D/def2TZVP/IEFPCM(*n*-hexane) level of theory. (**B**) Structural difference between *cis*- and *trans*-oxaphosphetanes.

versatile geminal *E*-bromofluoroalkenes could be prepared with excellent diastereoselectivity in a single step. This process is generally applicable to a wide variety of readily available carbonyl compounds including even some ketones and pharmaceutically relevant compounds. The operation of a kinetic control was confirmed by the quantitative ^{19}F NMR spectroscopic analysis of the reaction progress. Furthermore, the origin of such an intriguing phenomenon was rationalized by DFT calculation, which invoked the critical roles of the carbon-halogen bonds including distinctive dipole-dipole interaction as well as hyperconjugation with adjacent bonds. Currently, further scope expansion of this unique strategy to other halogens is ongoing in our laboratories.

MATERIALS AND METHODS

General experimental procedures

All reactions were performed in oven-dried (140°C) or flame-dried glassware under an atmosphere of dry argon unless otherwise noted.

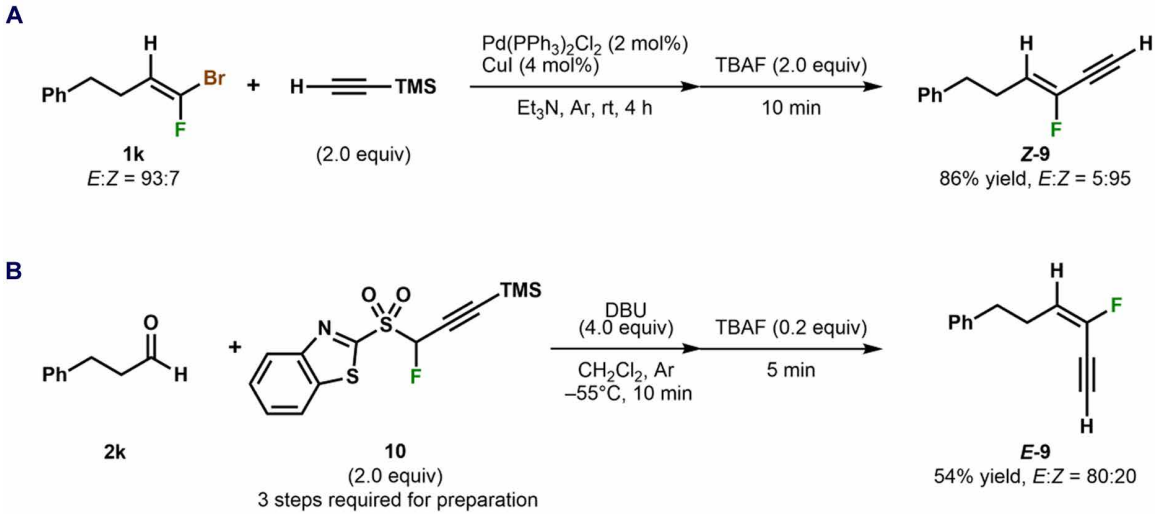


Fig. 5. Derivatization of geminal bromofluoroalkene. (**A**) Stereospecific Sonogashira coupling of **1k**. (**B**) Comparison with moderately selective, stereochemically complementary Julia olefination.

All the solvents and reagents were purified before use unless otherwise noted. See the Supplementary Materials for experimental details. ^{1}H, ^{13}C, ^{19}F, and ^{31}P NMR spectra were recorded on a JEOL ECS400 spectrometer (400 MHz, ^{1}H; 100 MHz, ^{13}C; 376 MHz, ^{19}F; 162 MHz, ^{31}P). Spectra are referenced to residual chloroform (7.26 ppm, ^{1}H; 77.16 ppm, ^{13}C), hexafluorobenzene (−161.64 ppm, ^{19}F), and triphenyl phosphate (−17.57 ppm, ^{31}P). Chemical shifts are reported in ppm (parts per million), and multiplicities are indicated by s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), and br (broad). Coupling constants, *J*, are reported in hertz. Kugelrohr distillation was carried out using Büchi B585 glass oven with Büchi bulb-to-bulb distillation apparatus, and air bath temperatures are reported. Filtration and column chromatography were performed using Merck 230–400 mesh silica gel. Preparative thin-layer chromatography (TLC) was performed using Analtech UNIPLATE 20 cm × 20 cm. Analytical TLC was conducted on Merck silica gel 60 F_{254} TLC plates. Visualization was accomplished with ultraviolet (254 nm) as well as a potassium permanganate ($KMnO_4$) staining solution. Electrospray ionization high-resolution mass spectrometry (ESI-HRMS) was performed on a Bruker Impact II quadrupole time-of-flight spectrometer at Gwangju Institute of Science and Technology (GIST) Advanced Institute of Instrumental Analysis. Electron ionization high-resolution mass spectrometry (EI-HRMS) was performed on a JEOL JMS-700 MStation mass spectrometer at Korea Basic Science Institute, Daegu Center. Data are reported in the form of mass/charge ratio (*m*/*z*).

General procedure for kinetically controlled stereoselective geminal bromofluoroolefination via selective conversion of oxaphosphetane intermediates

$PhP(Oi\text{-}Pr)_2$ (900 μl, 4.02 mmol) was added dropwise to a stirred mixture of a carbonyl compound (1.00 mmol) and $CFBr_3$ (195 μl, 1.99 mmol) in freshly distilled hexanes (2 to 5 ml) or toluene (5 ml) at 0°C in an ice bath under Ar. The reaction mixture was warmed to room temperature and stirred for 2 to 12 hours. Then, the reaction mixture was filtered through a silica gel pad with distilled hexanes. The filtrate was concentrated under reduced pressure to afford the geminal bromofluoroalkene. The *E*:*Z* ratio was determined by ^{19}F NMR analysis.

Supplementary Materials

The PDF file includes:
Supplementary Text
Figs. S1 to S11
Tables S1 and S2
Legend for data S1
Spectral Data
References

Other Supplementary Material for this manuscript includes the following:
Data S1

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