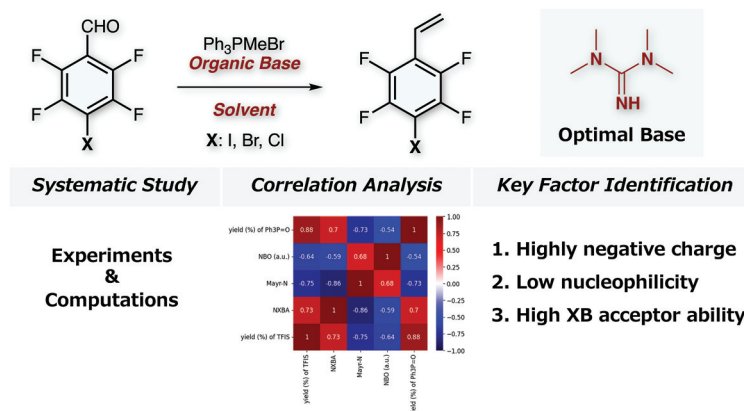


Synthesis of Halogen-Bond-Donor-Site-Introduced Functional Monomers through Wittig Reaction of Perfluorohalogenated Benzaldehydes: Toward Digitalization as Reliable Strategy in Small-Molecule Synthesis

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Aichi 444-8787, JapanThis paper is dedicated to Professor Hisashi Yamamoto in celebration of his 80th birthday.Published as part of the
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Abstract The Wittig reaction of perfluoromono-halobenzaldehydes was systematically studied to synthesize 2,3,5,6-tetrafluoro-4-halo-styrene (TFXSs) as functional monomers bearing halogen-bond donor sites. The reaction proceeded efficiently in tetrahydrofuran using 1,1,3,3-tetramethylguanidine as an organic base. Correlation analysis quantitatively identified three key factors required to obtain TFXSs in reasonable yields. The present approach not only contributes to the study of halogen-bond-based functional molecules, but also presents digitalization as a potential strategy in small-molecule synthesis.

Key words perfluorohalo styrenes, halogen bond, functional monomers, digitalization of organic synthesis, Wittig reaction

Halogen bonding (XB) is a unique noncovalent interaction between the Lewis acidic site of a halogen atom and the Lewis basic site of a molecule.¹ XB-driven smart polymer materials have recently attracted significant attention in polymer science.² In particular, iodoperfluorohydrocarbons³ are frequently used as XB donors. Among these, perfluorohalogenated styrenes are potential functional monomers, owing to their synthetic accessibility, donor tunability, and hydrophobicity. Takeuchi et al. reported molecularly

imprinted polymers with XB-based molecular recognition sites, in which 2,3,5,6-tetrafluoro-4-iodostyrene (TFIS) was used as the functional monomer (Figure 1a).⁴ Despite their potential utility, applications of 2,3,5,6-tetrafluoro-4-halo-styrene (TFXS)-derived synthetic polymers, including those of TFIS, have not been reported, except for the work of Takeuchi et al. This limitation is hypothesized to be due to the inherent volatility and instability of TFXSs, originating from their fluorine and halogen atoms. Furthermore, detailed synthesis of TFXS functional monomers by the Wittig reaction of perfluorohalogenated benzaldehydes has not been reported. This study reports the Wittig reaction of

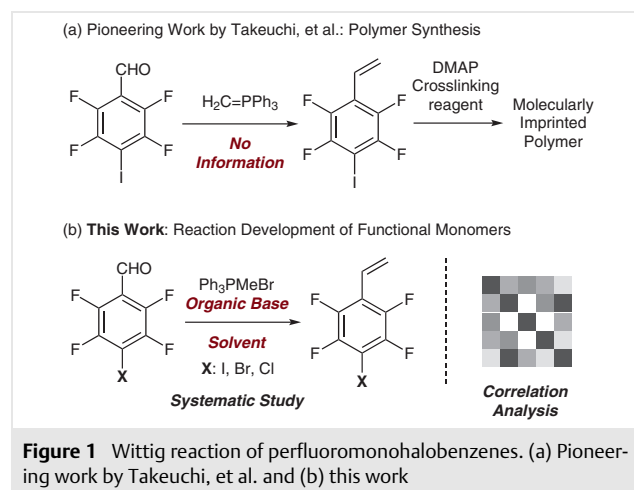


Table 1 Initial Study for the Wittig Reaction of **1a**^a

Entry	Ph ₃ PMeBr (equiv)	DBU (equiv)	Solvent	Temp ^b (°C)	Yield ^c (%)	
					2a	Ph ₃ P=O
1	1.2	1.2	CH ₂ Cl ₂	55	7	10
2	1.2	1.5	CH ₂ Cl ₂	55	8	12
3	2.4	3.0	CH ₂ Cl ₂	55	12	17
4	3.6	4.5	CH ₂ Cl ₂	55	11	24
5	3.6	4.5	THF	80	35	71
6	3.6	4.5	MeCN	95	<1	17
7	3.6	4.5	toluene	125	9	23
8	3.6	4.5	Et ₂ O	45	29	37
9	3.6	4.5	<i>t</i> -BuOMe	65	25	31
10	3.6	4.5	glyme	95	21	59
11	3.6	4.5	1,4-dioxane	115	11	76
12 ^d	3.6	4.5	THF	60	37	61
13 ^d	3.6	4.5	THF	40	27	44

^a Reactions conditions: **1a** (0.50 mmol), Ph₃PMeBr, DBU, solvent (6.5 mL), 2 h.

^b Set by the hotplate stirrer temperature controller under reflux conditions.
^c Yields were determined by ¹⁹F and ³¹P NMR with (trifluoromethyl)benzene and Ph₃P, respectively, as internal standards.

^d Reactions were performed at the indicated temperature.

perfluorohalogenated benzaldehydes, and provides insights into the key factors for obtaining TFXSs based on a correlation analysis, thereby permitting a quantitative understanding of the reaction and facilitating future research endeavors (Figure 1b).

Initially, the Wittig reaction of 2,3,5,6-tetrafluoro-4-iodobenzaldehyde (**1a**) was investigated at room temperature in tetrahydrofuran (THF) using conventional bases such as *n*-BuLi, *t*-BuOK, NaH, or K₂CO₃ (see Supporting Information). Although *n*-BuLi and *t*-BuOK produced triphenylphosphine oxide (Ph₃P=O) as an indicator of reaction progress (64% in the case of *n*-BuLi and 71% in the case of *t*-BuOK), the yields of TFXS (**2a**) were 31 and 34%, respectively, and multiple unidentified products were observed. In contrast, NaH and K₂CO₃ were unable to initiate the Wittig reaction to afford **2a** (<1%), and less than 10% Ph₃P=O was formed. In these cases, multiple unidentified products were detected, and **1a** was not fully recovered. Next, several organic bases were examined, and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) was selected as the organic base because had been reported to be useful for the Wittig reaction of electron-deficient aldehydes⁵ (Table 1). Careful examination under reflux conditions revealed that the choice of the

Table 2 Study of Organic Bases for the Wittig Reaction of **1a**^a

Entry	1	Base	pK _{BH} ^b	Temp ^c (°C)	Time (h)	Yield ^d (%)	
						2	Ph ₃ P=O
1	1a	TBD	20.1	60	2	8	33
2	1a	MTBD	18.0	60	2	36	56
3	1a	DBN	17.2	60	2	15	16
4	1a	DBU	16.9	60	2	37	61
5	1a	TMG	15.5	60	2	43	52
6	1a	piperidine	14.3	60	2	<1	<1
7	1a	quinuclidine	13.1	60	2	3	<1
8	1a	<i>i</i> -Pr ₂ EtN	12.7	60	2	<1	<1
9	1a	Et ₃ N	12.5	60	2	1	<1
10	1a	DABCO	11.7	60	2	<1	<1
11	1a	TMG	15.5	80	2	46	64
12	1a	TMG	15.5	80	4	51	69
13	1a	TMG	15.5	80	6	53	82
14	1a	TMG	15.5	80	24	54	80
15	1b	TMG	15.5	80	6	39	70
16	1b	TMG	15.5	80	6	29	73

^a Reaction conditions: **1** (0.50 mmol), Ph₃PMeBr (1.80 mmol), organic base (2.25 mmol), solvent (6.5 mL).¹⁰


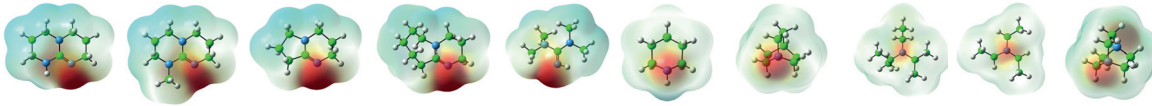
^b Leito and co-workers.⁷

^c Set by the hotplate stirrer temperature controller.

^d Determined by ¹⁹F and ³¹P NMR with (trifluoromethyl)benzene and Ph₃P, respectively, as internal standards.

solvent was more significant than the amount of the reagent (Ph₃PMeBr) or base (DBU) (Table 1, entries 1–11). In particular, the ether-type solvents afforded better yields of **2a** compared with CH₂Cl₂, toluene, or MeCN. THF was the best in suppressing unidentified products (entry 5), although the yield of **2a** was not sufficient. Moreover, when the reaction was conducted in THF, reflux was unnecessary (entries 12 and 13), and a temperature of 60 °C was sufficient to produce **2a** in a yield similar to that obtained under reflux conditions.

Table 3 Molecular Electrostatic Potential Maps, $V_{s,min}$, and NBO charges^a

										
MEPs										
Organic base	TBD	MTBD	DBN	DBU	TMG	piperidine	quinuclidine	<i>i</i> -Pr ₂ EtN	Et ₃ N	DABCO
$V_{s,min}$ (kJ/mol)	−187	−176	−200	−197	−187	−132	−140	−112	−118	−127
NBO (a.u.) ^b	−0.68	−0.67	−0.64	−0.64	−0.84	−0.73	−0.58	−0.62	−0.60	−0.57

^a DFT calculations were performed at the SMD(THF)/M06-2X-D3/6-311+G(d,p) level at 333 K.^b a.u. = atomic unit.**Table 4** Classifications of the Descriptors Used in the Correlation Analysis of the Organic-Base-Mediated Wittig Reaction of **1a**

Category	Descriptor	Physical meaning
reaction	yield (%) of Ph ₃ P=O	yield of triphenylphosphine oxide
	UDR-Pro	undesired reaction product ^a
	temp (°C)	reaction temperature
	time (h)	reaction time
	SVI-PC5 ^{13,14}	reaction solvent index
basicity center	pK _{BH}	basicity of organic base
	$V_{s,min}$ (kJ/mol)	electrostatic potential energy ^b
	NBO (a.u.)	NBO charge ^b
	delta G (kcal/mol)	ΔG: Gibbs free energy ^c
	Mayr-N	Mayr's nucleophilicity parameter
structure	NXBA	number of halogen bond acceptors
	cyclic/acyclic	structure of the organic base ^d
	NRing	number of rings in the organic base
	ring size of N	size of the ring with the basicity center ^e
	ring size of S	size of the ring without the basicity center ^f

^a Calculated according to the following equation: UDR-Pro (%) = 100 – [recovery yield of **1a** (%) + yield of **2a** (%)].^b For the nitrogen atom as the active center.^c For the protonation of an organic base.^d Equal to 1 if the structure is cyclic; equal to 0 if the structure is acyclic.^e Value = 0 if the active center is not in a ring.^f Value = 0 if the organic base lacks a ring structure or a ring structure.

To improve the yield of **2a**, several organic bases were investigated, based on their pK_{BH} values (Table 2).^{6–8} 1,5,7-Triazabicyclo[4.4.0]dec-5-ene (TBD), 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD), and 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) were found to be stronger bicyclic bases than DBU (entries 1–3). Importantly, MTBD afforded **2a** in a yield similar to that obtained in the presence of DBU, whereas TBD and DBN afforded **2a** in less than half the yield obtained in the presence of DBU. When bases weaker than DBU, such as 1,1,3,3-tetramethylguanidine (TMG), piperidine, quinuclidine, *N,N*-diisopropylethylamine (*i*-Pr₂EtN), triethylamine (Et₃N), and 1,4-diazabicyclo

[2.2.2]octane (DABCO), were used (entries 5–10), **2a** was obtained only with TMG (entry 5). Consequently, TMG was determined to be the best organic base among those tested in this study. After optimizing the reaction temperature and reaction time (entries 11–14), the best yield was achieved in the presence of TMG at 80 °C for six hours, where the yield Ph₃P=O, an important indicator of the reaction progress, attained 82% (entry 13). This reaction also enabled the production of 4-bromo-2,3,5,6-tetrafluorostyrene (TfBrS) (**2b**) and 4-chloro-2,3,5,6-tetrafluorostyrene (TfClS) (**2c**) in yields of 39% (entry 15) and 29%, respectively (entry 16). Overall, the yields of TFXS were approximately 30–55%;

however, considering the properties and inherent side reactions of the bases,⁹ the Wittig reaction of **1** mediated by TMG is an important finding that enables the production of TFXSs as functional monomers.

To identify the important factors for the production of TFXSs, density functional theory (DFT) calculations were performed. The molecular electrostatic potentials (MEPs) of organic bases in THF were mapped on the isodensity surface using the solvation model based on density (SMD), where the minimum negative electrostatic potential energies ($V_{s,min}$) and natural bond orbital (NBO) charges on the active nitrogen were quantitatively evaluated with regard to the activity of the organic bases (Table 3). The DFT calculations suggested that the production of TFXSs requires $V_{s,min}$ and NBO values of less than -175 kJ/mol and -0.60 a.u., respectively. Although basicity-related physicochemical indices, such as pK_{BH} , $V_{s,min}$, and NBO values, are useful in understanding the ylide formation in the Wittig reaction, they are insufficient to explain the superior utility of TMG compared with TBD, MTBD, DBN, or DBU.

To further elucidate the key factors that facilitate the organic-base-mediated Wittig reaction of **1**, correlation analyses were performed and heatmaps were created for visualization.¹¹ The descriptors were classified into three categories (Table 4; see Supporting Information): (i) reaction

parameters, (ii) basicity center parameters, and (iii) structure parameters. These feature parameters were used as the explanatory variables for the yields of TFIS **2a** as the objective variable in the correlation analyses. The variational Bayesian Gaussian mixture regression (VBGMR) machine-learning model was used to fill in the previously unreported pK_{BH} , the nucleophilicity parameter N ,¹² and the unavailable $V_{s,min}$ (kJ/mol), NBO (a.u.), and ΔG (kJ/mol) values (see Supporting Information). The key factors in the organic-base-mediated Wittig reaction are quantitatively discussed based on the absolute values of the correlation coefficients ($|r|$). The strength of correlations is determined according to the following magnitudes: very high, $0.9 < |r| < 1.0$; high, $0.7 < |r| < 0.9$; moderate, $0.5 < |r| < 0.7$; low, $0.3 < |r| < 0.5$; weak, $|r| < 0.3$.

The correlation analysis revealed that the yields of **2a** are highly correlated to the yield of triphenylphosphine oxide ($|r|$: 0.88) (Figure 2a, left). This clearly indicates that the ylide formation is of primary importance for the product formation of **2a**. The $|r|$ of the five reaction parameters to the yield of **2a** followed the order: yield (%) of $Ph_3P=O$ ($|r|$: 0.88) > time (h) ($|r|$: 0.44) > SVI-PC5 ($|r|$: 0.23) > UDR-Pro ($|r|$: 0.12) > temp ($^{\circ}C$) ($|r|$: 0.06) (Figure 2b, left). These results suggest that prolonging the reaction time and increasing the reaction temperature do not necessarily guarantee

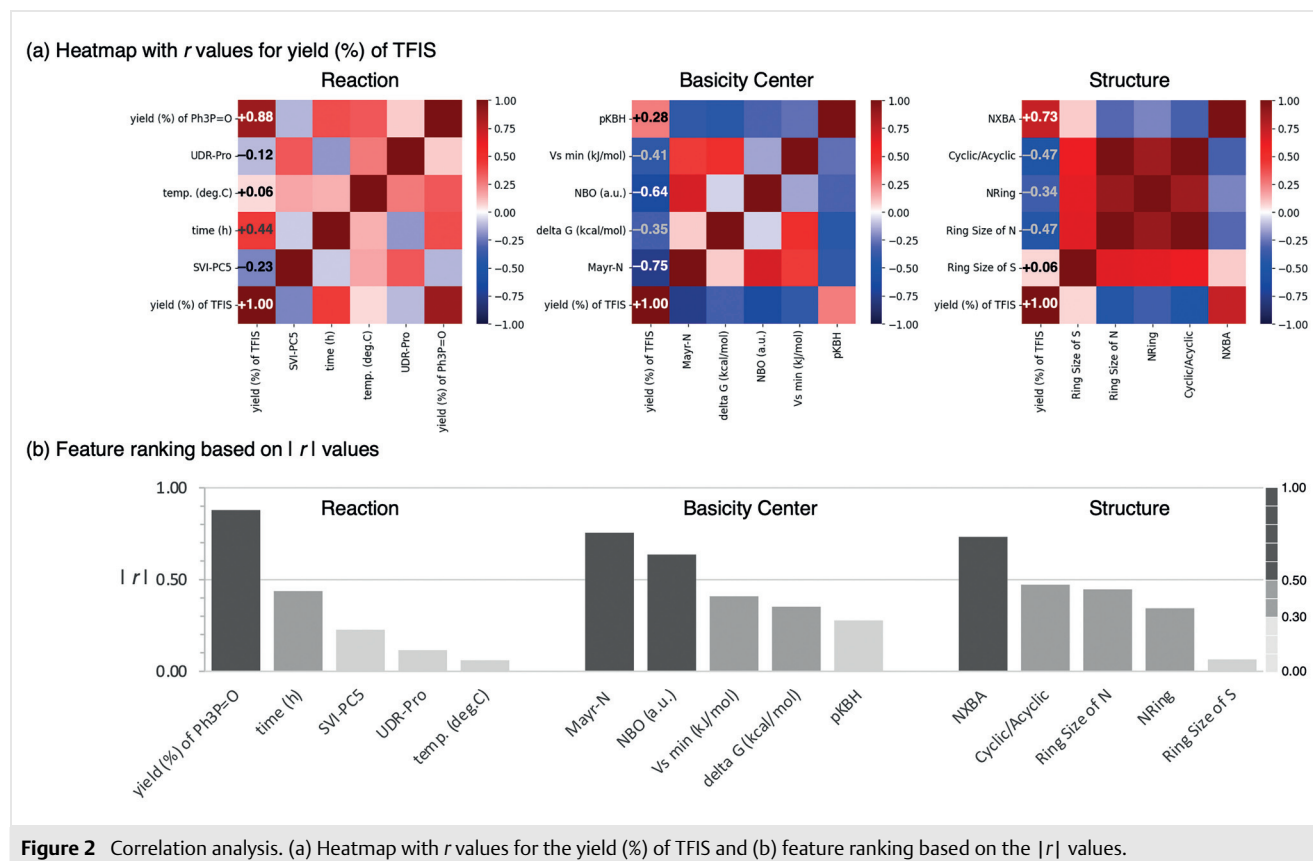


Figure 2 Correlation analysis. (a) Heatmap with r values for the yield (%) of TFIS and (b) feature ranking based on the $|r|$ values.

favorable outcomes. Among the descriptors of the basicity center, the nucleophilicity parameter (Mayr-N) exhibited a highly negative relationship with the yield of **2a** ($|r|$: 0.75). This indicates that nucleophilic organic bases might initiate the decomposition of **1a** and/or **2a** through nucleophilic attack, thereby leading to low yields of **2a**. This can explain why the low nucleophilicity of organic bases is of secondary importance in achieving better yields of **2a** (for example, 11.4 for TMG and 16.6 for DBN). $V_{s,min}$ and NBO exhibited moderate correlations with yields of **2a** ($|r|$: 0.64 for NBO, $|r|$: 0.41 for $V_{s,min}$) (Figure 2a, center), thereby indicating the importance of an appropriate basicity for initiating ylide formation. The third key factor is the number of halogen-bond acceptors (NXBA), which exhibited a strong positive relationship with **2a** yields ($|r|$: 0.73, Figure 2b, right). This provides a rational explanation for the assistance of XB between **2a** and organic bases in suppressing the decomposition of **2a** through complexation. In fact, NBO and $V_{s,max}$, the representative indicators for XB donor abilities of TFX-Ss, were markedly correlated to the yields (coefficients of determination R^2 : 0.99 for NBO and 0.96 for $V_{s,max}$) (see Supporting Information).

In summary, we have developed an organic-base-mediated Wittig reaction for the synthesis of TFXSs (**2**) from 2,3,5,6-tetrafluoro-4-halobenzaldehydes (**1**). Among the organic bases examined, TMG was found to be the most suitable. Correlation analysis quantitatively suggested the following are key factors: (i) a highly negative charge on the organic base for ylide formation, (ii) a low nucleophilicity of the organic base to suppress the decomposition of **1** and **2**, and (iii) and XB acceptor ability of the organic base for complexation with **2**. We believe that this study has the potential to become a practical example of digitalization in small-molecule synthesis.¹⁵ The ongoing application of TFXSs to XB-driven smart polymer materials in our laboratory will be presented in due course.

Conflict of Interest

The authors declare no conflict of interest.

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Supporting Information

Supporting information for this article is available online at <https://doi.org/10.1055/a-2118-6813>.

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- (10) **2,3,5,6-Tetrafluoro-4-iodostyrene (2a); Typical Procedure**
1,1,3,3-Tetramethylguanidine (282 μ L, 2.25 mmol, 4.5 equiv) was added to a solution of methyl(triphenyl)phosphonium bromide (0.643 g, 1.80 mmol, 3.6 equiv) in THF (5 mL) was added, and the resulting mixture was stirred at 80 °C for 30 min. A solution of 2,3,5,6-tetrafluoro-4-iodobenzaldehyde **1a** (0.152 g, 0.50 mmol, 1.0 equiv) in THF (1.5 mL) was added, and the resulting mixture was stirred for 6 h. Subsequently, H₂O (10 mL) was added to the mixture and the organic layer was separated. The aqueous layer was extracted with CH₂Cl₂ (3 \times 10 mL), and the combined organic layers were washed with brine (10 mL) and dried (MgSO₄). Small aliquots from the organic layers were

analyzed by ^{19}F NMR with PhCF_3 as a standard (NMR yield: 53%). The organic layers were concentrated under a reduced pressure to afford a colorless oil. Due to its instability, the product was characterized as a mixture, and full data could not be collected. $R_f = 0.53$ (hexane). IR (ATR): 1471, 1416, 1259, 1101, 983, 953, 794 cm^{-1} . ^1H NMR (400 MHz, CDCl_3): $\delta = 6.69$ (dd, $J = 11.9, 6.2$ Hz, 1 H), 6.15 (d, $J = 18.1$ Hz, 1 H), 5.76 (d, $J = 11.9$ Hz, 1 H). ^{19}F NMR (376 MHz, CDCl_3): $\delta = -121.65$ to -121.74 (m, 2 F), -141.56 to -141.66 (m, 2 F). ^{13}C NMR (^{19}F) (100 MHz, CDCl_3): $\delta = 147.2, 144.0$ (d, $J = 4.9$ Hz), 124.3 (t, $J = 160$ Hz), 122.3 (dd, $J = 163, 2.9$ Hz), 117.6–117.3 (m), 70.3.

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