New Synthesis of Diarylmethanes, Key Building Blocks for SGLT2 Inhibitors

Masahiko Seki,* Sandeep Ramesharao Tapkir, Maheshwara Reddy Nadiveedhi, Shaheen Kasim Mulani, and Kazushi Mashima*
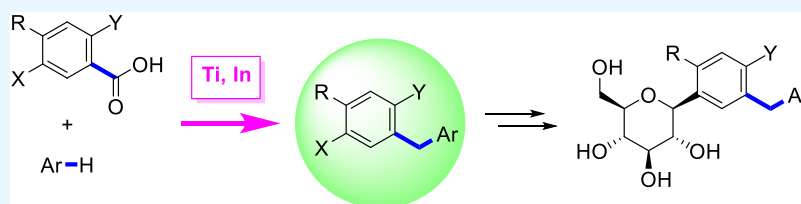
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ABSTRACT: Synthesis of diarylmethanes, a key building block for SGLT2 inhibitors, has been developed through ketone synthesis by Friedel−Crafts acylation with $TiCl_4$, followed by reduction with $TiCl_4$/$NaBH_4$. The new protocol proceeded more cleanly than the previous methods employing $AlCl_3$ and $BF_3 \cdot OEt_2$/Et_3SiH to provide the diarylmethanes corresponding to canagliflozin, empagliflozin, and luseogliflozin in a highly expedient and affordable manner. In the case of a diarylmethane for the synthesis of dapagliflozin, the reduction step took place by an alternative method using $InCl_3$/Al/$BF_3 \cdot OEt_2$.

INTRODUCTION

Diarylmethanes **1** have received keen interest as a significant building block for drugs and natural products (Figure 1).[1]
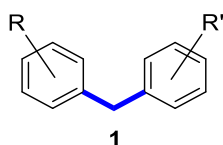

Figure 1. Diarylmethanes **1**.

Intensive research has been directed toward an efficient synthesis of this class of compounds including Friedel−Crafts benzylation of benzyl alcohols[2a] or benzyl halides[2b] or benzyl acetates or benzyl ammonium salts;[2c] Suzuki coupling of aryl boronic acids[2d] or benzyl boronic acids;[2e] Negishi coupling of benzyl zinc reagents;[2f] Kumada coupling of benzyl Grignard reagents;[2g] Stille coupling of benzyl tin reagents,[2h] and coupling of aromatic carboxylic acids[2i] (Scheme 1). Among them, synthesis using aromatic carboxylic acids **2**[2i] represents one of the major approaches to **1** because of commercial abundance of the carboxylic acids.[3]

In the meantime, as a part of our ongoing research program to develop an efficient and practical synthetic method for pharmaceuticals and their intermediates, we have undertaken the process development of SGLT2 inhibitors (sodium-glucose transporter 2 inhibitors) **3** due to their attractive medical efficacies such as a dual action for both diabetes and heart failure (Figure 2).[4] The compounds contain a characteristic

diarylmethane motif as a common structure in the molecules. Reported herein is a novel and efficient synthesis of diarylmethanes **1** in the SGLT2 inhibitors through Ti-based Friedel−Crafts acylation and reduction of the carbonyl group to methylene.

RESULTS AND DISCUSSION

For the synthesis of the diarylmethanes **1** leading to **3**, a well-documented approach is the method involving synthesis of diarylketones **5** followed by reduction of the carbonyl group to methylene (Scheme 2). Although the method has been implemented on a large commercial scale to meet the growing demand of **1**, they still have a drawback of employing expensive triethylsilane (reagent price: ca. US$153 per 1 mole of active hydride) as the reductant.[2i] To address this challenge, reported herein is an expedient synthesis of **1** by means of readily available $TiCl_4$-mediated Friedel−Crafts acylation and subsequent reduction of the resulting ketones with $TiCl_4$−$NaBH_4$ or $InCl_3$/$BF_3 \cdot OEt_2$/Al.
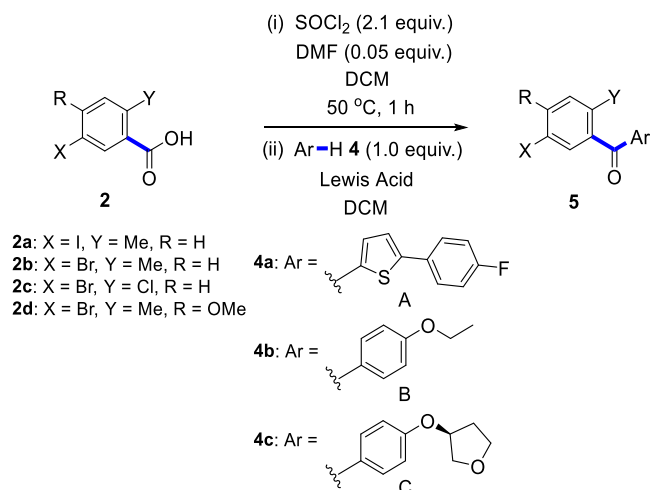
In our initial study, synthesis of diarylketones **5** from aromatic carboxylic acids **2** has been examined through Friedel−Crafts acylation of acid chlorides *in situ* generated

Scheme 1. Synthetic Approaches to Diarylmethanes 1

canagliflozin (**3a**)

dapagliflozin (**3b**)

empagliflozin (**3c**)

luseogliflozin (**3d**)

1a: X = I, Y = Me, R = H, Ar = A
1b: X = Br, Y = Me, R = H, Ar = A
1c: X = Br, Y = Cl, R = H, Ar = B
1d: X = Br, Y = Cl, R = H, Ar = C
1e: X = Br, Y = Me, R = OMe, Ar = B

Ar:

A

B

C

Figure 2. SGLT2 inhibitors **3a**−**d** and diarylmethane building blocks **1a**−**e**.

Scheme 2. Synthesis of Diarylmethanes 1 from Aromatic Carboxylic Acids 2

from **2** (Table 1).[2i,5] For a Lewis acid to effect the transformation, AlCl$_3$ is most widely employed for the aromatic substitution. Nonetheless, handling of the moisture-sensitive solid Lewis acid is problematic, especially on a large scale. Hence, as an alternative approach, the use of a readily available liquid TiCl$_4$ was tested. Thus, treatment of an acid

Table 1. Synthesis of Diarylketones 5 from Aromatic Carboxylic Acids 2

entry	compd	X	Y	R	Ar	Lewis acid (equiv)	temp. (°C)	time (h)	yield (%)[a]
1	5a	I	H	H	A	TiCl$_4$ (1.5)	0−30	4	91
2	5a	I	H	H	A	AlCl$_3$ (1.2)	5−25	2.5	89
3	5b	Br	H	H	A	TiCl$_4$ (1.5)	0−30	4	88
4[b]	5c	Br	Cl	H	B	TiCl$_4$ (1.5)	8−12	3.3	74
5	5d	Br	Cl	H	C	TiCl$_4$ (1.5)	0−50	16	39
6[c]	5e	Br	H	OMe	B	TiCl$_4$ (1.5)	5−25	2.3	80

[a]Isolated yield. [b]The acid chloride formation was conducted using oxalyl chloride (1.1 equiv) at 10−25 °C for 20 h. [c]The acid chloride formation was conducted using oxalyl chloride (1.1 equiv) in CHCl$_3$ at 6−25 °C for 12 h.

Table 2. Reduction of Diaryl Ketone 5a to Diaryl Methane 1a
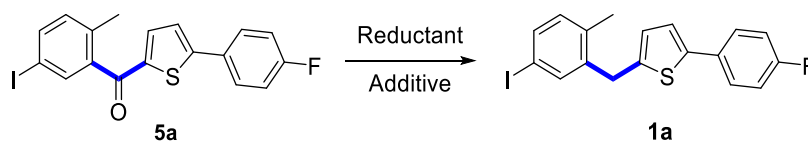
entry	reductant (equiv)	additive (equiv)	solvent (V)	temp. (°C)	time (h)	yield (%)[a]
1	Et$_3$SiH (4.0)	BF$_3$·OEt$_2$ (3.8)	DCM/CH$_3$CN (10:10)	0−25	4	41
2	TCS (4.0)	BF$_3$·OEt$_2$ (3.8)	CH$_3$CN (20)	50	5	NR[b]
3	PMHS (4.0)	BF$_3$·OEt$_2$ (3.8)	DME (20)	70	5	NR[b]
4	NaBH$_4$ (1.2)	H$_2$SO$_4$ (0.6)	THF (10)	50	3	NR[b]
5	NaBH$_4$ (1.0)	MgCl$_2$ (0.5)	diglyme (10)	50	3	[c]
6	NaBH$_4$ (1.0)	CaCl$_2$ (0.5)	DME (10)	50	3	[c]
7	NaBH$_4$ (1.0)	FeCl$_3$ (1.0)	DME (10)	50	3	[c]
8	NaBH$_4$ (1.0)	TiCl$_4$[d] (1.0)	DME (20)	70	3	64
9[e]	NaBH$_4$ (1.5)	TiCl$_4$[d] (1.0)	DME (10)	70	2	85
				50	5	

[a]Isolated yield. [b]No reaction. [c]The product was an alcohol 6a as shown below:
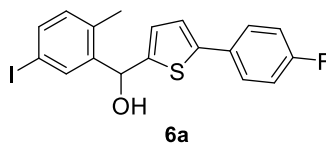
[d]Added as a 25 wt % of DCM solution. [e]Sequential treatment with NaBH$_4$ at 70 °C for 2 h and with TiCl$_4$ at 50 °C for 5 h.

chloride obtained from 5-iodo-2-methylbenzoic acid 2a with 2-(4-fluorophenyl)thiophene 4a in the presence of TiCl$_4$ was tested to provide the diarylketone 5a in 91% yield, which is comparable to the outcome with AlCl$_3$ (89%, Table 1, entries 1, 2). Although use of TiCl$_4$ for Friedel−Crafts acylation has been reported,[6] it was only applied to simple substrates. Functionalized substrates such as the present case has never been employed especially for the synthesis of SGLT2

inhibitors.[4a] Then, the method was applied to the synthesis of other diaryl ketones 5b−e including bromides for the synthesis of canagliflozin (3a), dapagliflozin (3b), empagliflozin (3c), and luseogliflozin (3d) (Table 1, entries 3−6) to give the corresponding diarylketones in moderate to high yields. The lower yield of empagliflozin intermediate 5d (39%) was owing to incomplete conversion with substrates remained intact. No formation of regioisomers was detected for all

reactions. Remarkably, in contrast to AlCl$_3$, operation of TiCl$_4$ in DCM was quite easy in terms of avoiding exposure to moisture, and after addition of the TiCl$_4$ solution to the reaction mixture, a homogeneous solution was maintained throughout the reaction.

Reduction of the diarylketones **5** to methylene derivatives **1** was our next subject for investigation. Combination of inexpensive reductants with various metal salts was tested using conversion of **5a** to **1a** as a typical example (Table 2). For a control experiment, a known procedure using Et$_3$SiH/ BF$_3$·OEt$_2$ was tested to provide the desired product **1a** in 41% yield (Table 2, entry 1).[7] Expecting cost reduction, either use of trichlorosilane (TCS) or polymethylhydrosilane (PMHS) in the presence of BF$_3$·OEt$_2$ was tried (Table 2, entries 2 and 3). However, no desired product **1a** was obtained with complete recovery of **5a**. As alternative approaches, use of inexpensive NaBH$_4$ (reagent price: ca. US$7.7 per 1 mole of active hydride) in the presence of Brønsted acid (H$_2$SO$_4$) or Lewis acid (MgCl$_2$, CaCl$_2$, FeCl$_3$) was attempted (Table 2, entries 4−7). Contrary to our expectation, no reaction or formation of alcohol **6a** resulted. Finally, the TiCl$_4$/NaBH$_4$ system was tested (Table 2, entry 8). To our delight, by the treatment, the desired product **1a** was obtained in 64% yield. Finally, sequential reduction of **5a** with NaBH$_4$ (1.5 equiv) at 70 °C for 2 h to alcohol **6** followed by reaction with TiCl$_4$ (1.5 equiv) at 50 °C for 5 h provided **1a** in 85% yield (Table 2, entry 9). It should be noted that addition of TiCl$_4$ to the mixture resulted in no raise in temperature and heating up was needed to reach 50 °C. Hence, as far as for the scale of the reaction indicated, there is no concern about any significant exothermic reaction on adding TiCl$_4$.

The reduction protocol was applied to the synthesis of diarylmethanes (**1b** (bromide), **1c**, **1d**, **1e**) for canagliflozin (**3a**), empagliflozin (**3c**), and luseogliflozin (**3d**) to give the desired products in good yields (Table 3, entries 1, 3, and 4). In marked contrast, when reduction of diarylketone (**5c**) corresponding to dapagliflozin (**3b**) was examined, the reaction gave a dimer **7c** (Table 3, entry 2).[8]

For reduction of **5c**, another protocol using InCl$_3$/Al/BF$_3$· OEt$_2$[9] was tested to furnish the desired diarylmethane **1c** in 56% yield (Scheme 3).

A possible reaction mechanism for TiCl$_4$/NaBH$_4$ reduction of diarylketone **5** to diarylmethane **1** is shown in Scheme 4. To begin with, benzyl alcohol **6** is generated by treatment of **5** with NaBH$_4$.[10] Then, benzylic carbocation **8** is formed from **6** by addition of TiCl$_4$. Subsequent single electron transfer (SET) produces benzylic radical **9**, which produces diarylmethane **1** through another SET and protonation. Switch of the product from **1c** to the dimer **7c** was observed for the reaction starting from **5c**. This might be accounted for by a subtle difference in stabilities of the benzylic radicals, but the detailed reasons behind this remain unclear.[11]
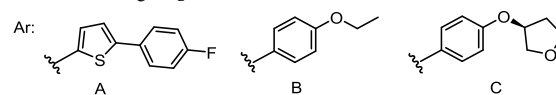
CONCLUSIONS

An alternative synthesis of diarylmethanes has been worked out by using TiCl$_4$-mediated Friedel−Crafts acylation and reduction of the resulting diarylketones either by TiCl$_4$/ NaBH$_4$ or InCl$_3$/Al/BF$_3$·OEt$_2$ depending on the substrate employed. The entire procedure can be carried out using readily available and cheap reagents under mild reaction conditions. The scale-up studies such as precise evaluation of the quality of the products, safety assessment, telescoping of the reaction sequence, and removal of silica gel column

Table 3. Reduction of Diaryl Ketone 5b−e to Diarylmethane 1b−e with NaBH$_4$/TiCl$_4$

entry	compd	X	Y	R	Ar[a]	temp (°C)	time (h)	yield (%)[c]
1[c]	1b	Br	Me	H	A	65−70	3	86
						45−50	5	
2[d]	1c	Br	Cl	H	B	50	0.2	96[e]
						50	2	
3[c]	1d	Br	Cl	H	C	65−70	2	79
						45−50	6	
4[f]	1e	Br	Me	OMe	B	70	2	79
						40	7	

[a]Structures of Ar groups:

[b]Isolated yields. [c]Sequential treatment with NaBH$_4$ at 65−70 °C and with TiCl$_4$ at 45−50 °C. [d]Sequential treatment with NaBH$_4$ at 50 °C and with TiCl$_4$ at 50 °C. [e]The product was not **1c** but a dimer **7c** as shown below:
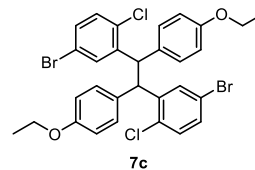
[f]Sequential treatment with NaBH$_4$ at 70 °C and with TiCl$_4$ at 40 °C.

chromatography purification are under current investigation, which will be reported elsewhere in due course.

■ EXPERIMENTAL SECTION

General. ^{1}H, ^{13}C, and ^{19}F NMR spectra (JEOL JNM-LA 500 spectrometer, 500, 126, and 376 MHz, respectively) were recorded with tetramethylsilane used as an internal standard. Melting points were determined using a Büchi (Model M565) automated melting point system (temperature measurement accuracy is 0.1 °C). High-resolution mass spectrometry was performed by the Elemental Analysis Section of Osaka University. Thin-layer chromatography (TLC) was carried out on E. Merck 0.25 mm pre-coated glass-backed plates (60 F$_{254}$). Development was accomplished using 5% phosphomolybdic acid in ethanol with heating or visualized by UV light where feasible. Column chromatography was performed with SiO$_2$ (Silica Flash F60, 230−400 mesh). All solvents and reagents were used as received.

Typical Procedure for Synthesis of Diarylketone 5. *(5-(4-Fluorophenyl)-thiophen)-2-yl-(5-iodo-2-methylphenyl)-methanone (5a).*[7] To a suspension of 5-iodo-2-methylbenzoic acid **2a** (5.00 g, 19.1 mmol) in CH$_2$Cl$_2$ (35 mL) was added DMF (0.0700 g, 0.950 mmol) followed by SOCl$_2$ (4.77 g, 40.1 mmol) at 20−30 °C. The mixture was stirred at 50 °C for 1 h under an argon atmosphere. Progress of the reaction was monitored through TLC by quenching with MeOH. The reaction mixture was evaporated, and the residue was dissolved in CH$_2$Cl$_2$ (35 mL). A solution of TiCl$_4$ (5.43 g, 28.6 mmol)

Scheme 3. Reduction of Diarylketone 5c to Diarylmethane 1c with InCl$_3$/Al/BF$_3$·OEt$_2$
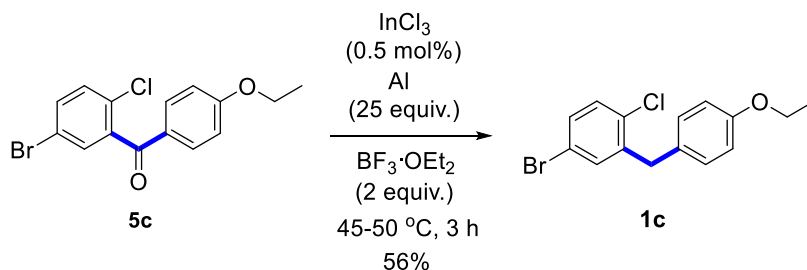
Scheme 4. Possible Mechanism for TiCl$_4$/NaBH$_4$ Reduction of Diarylketones 5 to Diarylmethanes 1
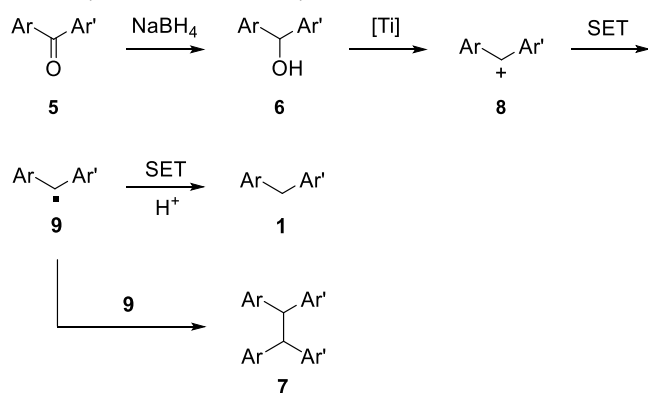
in CH$_2$Cl$_2$ (17.5 mL) was added to the mixture at 0−10 °C, and the mixture was stirred at the same temperature for 30 min. Then, a solution of 2-(4-fluorophenyl)thiophene (**4a**)[10] (3.40 g, 19.1 mmol) in CH$_2$Cl$_2$ (17.5 mL) was added to the above mixture at 0−10 °C and further stirred at 20−30 °C for 4 h. After quenching the reaction by addition of water (50 mL), the reaction mixture was extracted with CH$_2$Cl$_2$ (2 × 25 mL). Combined CH$_2$Cl$_2$ extracts were washed with water (2 × 25 mL) followed by sat. aq. NaHCO$_3$ (2 × 25 mL), dried over sodium sulfate, evaporated to give a crude **5a** as a light brown solid (8.8 g). Trituration of the crude **5a** in heptane (50 mL) provided pure **5a** (7.30 g, 91%) as a light brown solid. MP: 138−142 °C; IR (NaCl) ν_{max}: 1638, 1612, 1530, 1441, 1294, 1235, 1160, 1059, 813 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.75 (d, J = 1.9 Hz, 1H), 7.70 (dd, J = 8.1, 1.9 Hz, 1H), 7.67−7.61 (m, 2H), 7.36 (d, J = 4.0 Hz, 1H), 7.25 (d, J = 3.9 Hz, 1H), 7.15−7.09 (m, 2H), 7.04 (d, J = 8.1 Hz, 1H), 2.32 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ: 188.23, 163.30 (d, $^1J_{C-F}$ = 250.74 Hz), 153.27, 142.69, 140.32, 139.07, 136.81, 136.18, 135.98, 132.93, 129.43 (d, $^4J_{C-F}$ = 3.7 Hz), 128.19 (d, $^3J_{C-F}$ = 8.4 Hz), 124.09 (d, $^5J_{C-F}$ = 1.6 Hz), 116.26 (d, $^2J_{C-F}$ = 22.68 Hz), 89.62, 19.28; ^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$, 30 °C) δ: −111.16.

(5-(4-Fluorophenyl)-thiophen)-2-yl-(5-bromo-2-methylphenyl)methanone (5b).[7] The compound was prepared according to the typical procedure for the synthesis of **5a** using 5-bromo-2-methylbenzoic acid **2b** (5.00 g, 23.3 mmol), SOCl$_2$ (5.80 g, 48.8 mmol), TiCl$_4$ (6.62 g, 34.9 mmol), and 2-(4-fluorophenyl)thiophene **4a** (4.14 g, 23.2 mmol). Yield: 7.70 g (88%) as a pale-yellow solid. MP: 122−126 °C; IR (NaCl) ν_{max}: 1639, 1599, 1531, 1504, 1442, 1296, 1257, 1235, 1161, 1059 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.67−7.61 (m, 2H), 7.57 (d, J = 2.2 Hz, 1H), 7.50 (dd, J = 8.2, 2.1 Hz, 1H), 7.37 (d, J = 4.0 Hz, 1H), 7.25 (d, J = 4.0 Hz, 1H), 7.17 (d, J =

8.1 Hz, 1H), 7.15−7.09 (m, 2H), 2.33 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ: 188.36, 163.30 (d, $^1J_{C-F}$ = 250.74 Hz), 153.29, 142.64 (d, $^5J_{C-F}$ = 0.9 Hz), 139.97, 136.81, 135.35, 133.12, 132.71, 130.45, 129.41 (d, $^4J_{C-F}$ = 3.7 Hz), 128.18 (d, $^3J_{C-F}$ = 8.4 Hz), 124.08 (d, $^5J_{C-F}$ = 1.6 Hz), 118.76, 116.25 (d, $^2J_{C-F}$ = 22.68 Hz), 19.17; ^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$, 30 °C) δ: −111.15.

(5-Bromo-2-chlorophenyl)(4-ethoxyphenyl)methanone (5c).[12] To a suspension of 5-bromo-2-chlorobenzoic acid (**2c**) (5.00 g, 21.2 mmol) in CHCl$_3$ (60 mL) was added DMF (0.0150 g, 0.200 mmol). Then, oxalyl chloride (2.96 g, 23.3 mmol) was added at 10 °C, and the mixture was stirred at 25 °C for 20 h. The mixture was evaporated, and the residue was dissolved in CH$_2$Cl$_2$ (20 mL). To the solution was added TiCl$_4$ (6.04 g, 31.8 mmol) in CH$_2$Cl$_2$ (20 mL) at 10 °C over 3 min, and the mixture was stirred at 10 °C for 15 min. To the solution was added phenetole **4b** (2.59 g, 21.2 mmol) at 8−12 °C over 15 min, and the mixture was stirred at the same temperature for 3 h. To the mixture was added water (20 mL). The aqueous phase was extracted with CH$_2$Cl$_2$ (20 mL) and the combined organic phases were washed with water (20 mL), dried over MgSO$_4$, and evaporated to give crude **5c** (7.1 g), which was subjected to recrystallization using hexane (30 mL) to obtain pure **5c** as a colorless solid (5.30 g, 74%). MP: 68−70 °C; IR (NaCl) ν_{max}: 1736, 1659, 1595, 1244 cm^{-1}; ^{1}H NMR (500 MHz) δ: 7.75 (d, J = 8.7 Hz, 1H), 7.53−7.48 (m, 1H), 7.46 (dd, J = 2.2, 0.8 Hz, 1H), 7.30 (dd, J = 8.6, 0.7 Hz, 1H), 6.93−6.89 (m, 2H), 4.09 (q, J = 7.0 Hz, 1H), 1.42 (t, J = 7.0 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz) δ: 192.13, 163.95, 140.78, 133.78, 132.67, 131.62, 131.53, 130.17, 128.65, 120.59, 114.56, 64.04, 14.74.

(S)-(5-Bromo-2-chlorophenyl)(4-((tetrahydrofuran-3-yl)-oxy)phenyl)methanone (5d).[13] The compound was prepared according to the typical procedure for the synthesis of **5a** using 5-bromo-2-methylbenzoic acid **2b** (0.500 g, 2.12 mmol) in CH$_2$Cl$_2$ (3.5 mL), DMF (7.76 mg, 0.106 mmol), SOCl$_2$ (0.530 g, 4.46 mmol), TiCl$_4$ (0.60 g, 3.18 mmol), and (S)-3-phenoxytetrahydrofuran **4c** (0.418 g, 2.55 mmol) under the conditions described in Table 1. The crude **5d** was purified by silica gel column chromatography (hexane/ethyl acetate 9.5:0.5 to 6:4) to afford pure **5d** (0.316 g, 39%) as a colorless sticky oil. IR (NaCl) $\nu_{\mu max}$: 3058, 2980, 2953, 2867, 1668, 1661, 1598, 1572, 1506, 1456, 1423, 1251, 1084, 845, 736 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.79−7.67 (m, 2H), 7.51 (dd, J = 8.5, 2.4 Hz, 1H), 7.45 (d, J = 2.4 Hz, 1H), 7.29 (d, J = 8.5 Hz, 1H), 6.97−6.81 (m, 2H), 4.98 (ddt, J = 6.1, 4.1, 1.9 Hz, 1H), 4.04−3.92 (m, 3H), 3.88 (td, J = 8.4, 4.3 Hz, 1H), 2.31−2.19 (m, 1H), 2.17−2.09 (m, 1H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ: 191.85, 162.14, 140.42, 133.65, 132.48, 131.40, 131.35, 129.94, 128.79, 120.40, 115.10, 77.72, 72.83, 67.07, 32.86.

(5-Bromo-4-methoxy-2-methylphenyl)(4-ethoxyphenyl)-methanone (5e).[14] To a suspension of 5-bromo-4-methoxytoluic acid (3.00 g, 12.2 mmol) in CHCl$_3$ (36 mL) was added DMF (1 drop). To the mixture was added dropwise oxalyl chloride (1.71 g, 13.5 mmol) at 6 °C over 2 min. The mixture was stirred at the same temperature for 2 h and at 25 °C for 10 h. The mixture was evaporated, and the residue was dissolved in CH$_2$Cl$_2$ (12 mL). Then, TiCl$_4$ (3.50 g, 18.5 mmol) in CH$_2$Cl$_2$ (12 mL) was added at 10−12 °C over 5 min. The mixture was stirred at the same temperature for 15 min, and phenetole (1.50 g, 12.3 mmol) was added at 5−8 °C over 15 min. The mixture was stirred at the same temperature for 2 h and at 25 °C for 2 h. The mixture was poured into ice water (20 mL). The organic phase was separated and evaporated. To the residue was added hexane (30 mL) and the mixture was stirred at 5−10 °C for 1 h. The solid formed was filtered to give **5e** as a white solid (3.40 g, 80%). MP: 83.0 °C. IR (KBr) ν_{max}: 2938, 1641, 1601, 1591, 1572 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$, 30 °C) δ: 7.75 (d, J = 9.0 Hz, 2H), 7.51 (s, 1H), 6.93 (d, J = 9.0, 2H), 6.79 (s, 1H), 4.11 (q, J = 7.0 Hz, 2H), 3.95 (s, 3H), 2.33 (s, 3H), 1.45 (t, J = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (126 MHz) δ: 195.69, 163.56, 157.33, 139.22, 134.22, 132.93, 130.88, 114.71, 114.65, 114.63, 108.19, 64.30, 56.79, 20.81, 15.15.

Typical Procedure for Synthesis of Diarylmethane 1. *2-(4-Fluorophenyl)-5-(5-iodo-2-methylbenzyl)thiophene (1a).*[7] To a solution of (5-(4-fluorophenyl)-thiophen)-2-yl-(5-iodo-2-methylphenyl)methanone (**5a**) (100 mg, 0.240 mmol) in DME (1 mL) was added NaBH$_4$ (14.0 mg, 0.370 mmol) and the mixture was stirred at 70 °C for 2 h. Then, the mixture was cooled down to 25 °C, and TiCl$_4$ (67.0 mg, 0.350 mmol) in CH$_2$Cl$_2$ (0.2 mL) was added over 1 min, and the mixture was stirred at 50 °C for 5 h. The mixture was cooled down to 25 °C, water (5 mL) was added and the mixture was stirred for 30 min. The mixture was extracted with CHCl$_3$ (10 mL), and the organic phase was washed with water (2 × 5 mL) and evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 20:1) to give **1a** as a white solid (83.2 mg, 85%). MP: 106−110 °C; IR (NaCl) ν_{max}: 1509, 1480, 1440, 1232, 1159, 1098, 832, 800 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.57 (d, J = 1.5 Hz, 1H), 7.50 (dt, J = 8.1, 2.3 Hz, 3H), 7.09−7.01 (m, 3H), 6.93 (d, J = 8.0 Hz, 1H), 6.68 (d, J = 3.5 Hz, 1H), 4.06 (s, 2H), 2.28 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ: 162.05 (d, $^1J_{C-F}$ = 246.96 Hz), 142.20 (d, $^5J_{C-F}$ = 1.1 Hz), 141.73, 140.54, 138.01, 136.00, 135.90, 132.32, 130.64 (d, $^4J_{C-F}$ = 3.5 Hz), 127.08 (d, $^3J_{C-F}$ = 8.0 Hz), 126.15, 122.66 (d, $^5J_{C-F}$ = 1.7 Hz), 115.69 (d, $^2J_{C-F}$ = 21.42 Hz), 90.99, 33.63, 19.08; ^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$, 30 °C) δ: −116.3.

(5-(4-Fluorophenyl)thiophen-2-yl)(5-iodo-2-methylphenyl)methanol (6a).[15] NaBH$_4$ (0.13 g, 3.56 mmol) was added to a solution of (5-(4-fluorophenyl)thiophen-2-yl)(5-iodo-2-methylphenyl)methanone **5a** (1.00 g, 2.37 mmol) in DME (10 mL) at 20−30 °C. The mixture was heated to 65−70 °C for 3 h. After cooling the mixture to 20−30 °C, the reaction was quenched by addition of water (10 mL). The mixture was extracted with CH$_2$Cl$_2$ (2 × 10 mL). Combined CH$_2$Cl$_2$ extracts were washed with water (10 mL) and sat. aq. NaHCO$_3$ (10 mL), dried over sodium sulfate and evaporated to give crude compound **6**. Trituration of the crude **6a** with a mixture of heptane and Et$_2$O provided pure **6a** (0.920 g, 92%) as a yellow solid. MP: 111−115 °C; IR (NaCl) ν_{max}: 1508, 1472, 1458, 1232, 1159, 1097, 833, 806 cm^{-1}; ^{1}H NMR (500

MHz, DMSO-d_6) δ: 7.87 (d, J = 1.9 Hz, 1H), 7.65−7.56 (m, 2H), 7.50 (dd, J = 7.9, 2.0 Hz, 1H), 7.23 (d, J = 3.7 Hz, 1H), 7.20−7.13 (m, 2H), 6.95−6.90 (m, 1H), 6.77 (dd, J = 3.7, 0.8 Hz, 1H), 6.29 (s, 1H), 5.97 (s, 1H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6) δ: 161.74 (d, $^1J_{C-F}$ = 244.44 Hz), 148.14, 145.25, 141.63, 135.99, 134.65, 134.51, 132.76, 130.59 (d, $^4J_{C-F}$ = 3.2 Hz), 127.34 (d, $^3J_{C-F}$ = 8.1 Hz), 126.07, 123.27 (d, $^5J_{C-F}$ = 0.8 Hz), 116.12 (d, $^2J_{C-F}$ = 21.42 Hz), 91.63, 67.25, 18.60.

Synthesis of 2-(4-Fluorophenyl)-5-(5-iodo-2-methylbenzyl)thiophene (1a) from (5-(4-Fluorophenyl)-thiophen-2-yl)(5-iodo-2-methylphenyl)methanol (6a). NaBH$_4$ (13.0 mg, 0.340 mmol) was added to a solution of (5-(4-fluorophenyl)thiophen-2-yl)(5-iodo-2-methylphenyl)methanol (**6a**) (50.0 mg, 0.120 mmol) in DME (1 mL) at 25 °C. Then, TiCl$_4$ (67.0 mg, 0.350 mmol) in CH$_2$Cl$_2$ (0.140 mL) was slowly added, and the mixture was stirred at 50 °C for 3 h. To the mixture was added water (5 mL), and the mixture was stirred at 25 °C for 30 min. The mixture was extracted with AcOEt (3 mL), dried over MgSO$_4$, and evaporated. The residue was purified by silica gel column chromatography (hexane/AcOEt = 20:1) to give **1a** as a white solid (37.5 mg, 78%). The analytical data were the same as those of **1a** obtained from **5a**.

2-(4-Fluorophenyl)-5-(5-bromo-2-methylbenzyl)-thiophene (1b).[7] The compound was prepared according to the typical procedure for the synthesis of **1a** using (5-(4-fluorophenyl)-thiophen-2-yl)-(5-bromo-2-methylphenyl)-methanone (**5b**) (1.00 g, 2.66 mmol), NaBH$_4$ (0.15 g, 4.00 mmol), and TiCl$_4$ (0.76 g, 4.00 mmol) under the conditions described in Table 3. Trituration of crude **1b** in methanol provided pure **1b** (0.83 g, 86%) as an off-white solid. MP: 102−106 °C; IR (NaCl) ν_{max}: 1592, 1548, 1509, 1483, 1471, 1231, 1097, 865, 829, 798 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.54−7.47 (m, 2H), 7.37 (d, J = 1.8 Hz, 1H), 7.32 (dd, J = 8.1, 2.0 Hz, 1H), 7.11−7.00 (m, 4H), 6.69 (d, J = 3.5 Hz, 1H), 4.09 (s, 2H), 2.29 (s, 3H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ: 162.07 (d, $^1J_{C-F}$ = 246.96 Hz), 142.12 (d, $^5J_{C-F}$ = 1.2 Hz), 141.78, 140.29, 135.25, 132.09, 132.00, 130.65 (d, $^4J_{C-F}$ = 3.6 Hz), 129.84, 127.08 (d, $^3J_{C-F}$ = 8.1 Hz), 126.22, 122.67 (d, $^5J_{C-F}$ = 1.7 Hz), 119.61, 115.69 (d, $^2J_{C-F}$ = 21.42 Hz), 33.76, 18.97; ^{19}F{^{1}H} NMR (376 MHz, CDCl$_3$, 30 °C): −114.75.

(S)-3-(4-(5-Bromo-2-chlorobenzyl)phenoxy)-tetrahydrofuran (1d).[13] The compound was prepared according to the typical procedure for the synthesis of **1a** using (S)-(5-bromo-2-chlorophenyl)(4-((tetrahydrofuran-3-yl)oxy)phenyl)methanone (**5d**) (0.100 g, 0.262 mmol), NaBH$_4$ (14.9 mg, 0.393 mmol), and TiCl$_4$ (75.0 mg, 0.393 mmol) under the conditions described in Table 3. Crude **1d** was purified by silica gel column chromatography (hexane/ethyl acetate 9.5:0.5 to 6:4) to afford pure **1d** (76.1 mg, 79%) as a white solid. MP: 48−52 °C; IR (NaCl) ν_{max}: 2980, 2867, 2355, 1610, 1582, 1507, 1464, 1436, 1352, 1240, 1131, 1116, 971, 812 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ: 7.30−7.24 (m, 2H), 7.23−7.18 (m, 1H), 7.12−7.07 (m, 2H), 6.84−6.76 (m, 2H), 4.88 (d, J = 2.8 Hz, 1H), 4.02−3.95 (m, 5H), 3.92−3.86 (m, 1H), 2.22−2.10 (m, 2H); ^{13}C{^{1}H} NMR (126 MHz, CDCl$_3$) δ (ppm): 155.90, 141.00, 133.34, 132.88, 130.70, 130.64, 130.40, 129.86, 120.30, 115.28, 77.08, 72.91, 66.99, 37.98, 32.83.

1-Bromo-5-(4-ethoxybenzyl)-2-methoxy-4-methylben-zene (1e).[14] The compound was prepared according to the typical procedure for the synthesis of **1a** using (5-bromo-4-

methoxy-2-methylphenyl)(4-ethoxyphenyl)methanone (**5e**) (8.10 g, 23.2 mmol), $NaBH_4$ (1.30 g, 34.4 mmol), and $TiCl_4$ (6.58 g, 34.7 mmol) under the conditions described in Table 3. Crude **1e** was purified by silica gel column chromatography (ethyl acetate). Product **1e** obtained was dissolved at 50 °C in heptane (20 mL). The mixture was cooled down to 25 °C over 30 min and stirred at 5−10 °C for 2 h. The solid formed was filtered and washed with cooled heptane (5 mL) to give pure **1e** as a white solid (6.10 g, 79%). MP: 65.0 °C; IR (KBr) ν_{max}: 2976, 1514, 1491, 1248, 1045 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$, 30 °C) δ: 7.24 (s, 1H), 6.98 (d, J = 8.7 Hz, 2H), 6.78 (d, J = 8.6 Hz 2H), 6.69 (s, 1H), 3.98 (q, J = 7.0 Hz, 2H), 3.84 (s, 3H), 3.80 (s, 2H), 2.18 (s, 3H), 1.38 (t, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (126 MHz) δ: 57.41, 154.18, 137.20, 134.25, 133.27, 132.00, 129.61, 129.51, 114.56, 114.23, 63.49, 56.36, 37.65, 19.92, 15.02.

*Attempt to Obtain 1-Bromo-4-chloro-5-(4-ethoxybenzyl)-benzene (**1c**) Using TiCl$_4$/NaBH$_4$.* To a solution of (5-bromo-2-chlorophenyl)(4-ethoxyphenyl)methanone (**5c**) (1.00 g, 2.94 mmol) in DME (10 mL) was added NaBH$_4$ (0.220 g, 5.82 mmol), and the mixture was stirred at 50 °C for 10 min (foaming observed). Then, the mixture was cooled down to 25 °C, and TiCl$_4$ (1,12 g, 1.12 mmol) in CH$_2$Cl$_2$ (2 mL) was added over 1 min, and the mixture was stirred at 50 °C for 2 h. The mixture was cooled down to 25 °C, and water (30 mL) was added. The mixture was evaporated to remove organic solvent and extracted with AcOEt (2 × 15 mL). The combined organic phases were combined, washed with water (15 mL), dried over MgSO$_4$, and evaporated. The residue was purified by silica gel column chromatography (AcOEt) to give 1,2-bis(5-bromo-2-chlorophenyl)-1,2-bis(4-ethoxyphenyl)ethane (**7c**) (0.93 g, 97%) as an off-white semisolid. IR (NaCl) ν_{max}: 2925, 1612, 1582, 1511 cm^{-1}; ^{1}H NMR (500 MHz), δ: 7.55 (s, 2H), 7.13−7.02 (m, H), 6.67 (d, J = 7.9 Hz, 4H), 5.21 (s, 2H), 3.90 (q, J = 7.0 Hz, 4H), 1.34 (td, J = 6.9, 0.8 Hz, 6H). ^{13}C{^{1}H} NMR (125 MHz) δ: 157.57, 142.67, 132.77, 132.29, 131.62, 131.02, 130.55, 129.63, 120.70, 114.37, 77.37, 77.12, 76.86, 63.31, 50.37, 14.91. HRMS: [M + H]$^+$ calcd for $C_{30}H_{27}Br_2Cl_2O_2$ 649.9768, found 650.0461.

*1-Bromo-4-chloro-5-(4-ethoxybenzyl)benzene (**1c**).*[16] In a 25 mL round-bottom flask were placed 2-propanol (1.50 mL) and (5-bromo-2-chlorophenyl)(4-ethoxyphenyl)methanone (**5c**) (250 mg, 0.740 mmol), and the mixture was warmed to 50 °C. To this was added BF$_3$·Et$_2$O (0.180 mL, 1.47 mmol) followed by finely shredded aluminum foil (Nippaku Foil, Mitsubishi Aluminium Corporation, 496 mg, 18.4 mmol). Then, to the mixture was added indium(III) chloride (0.800 mg, 0.04 mmol) dissolved in 2-propanol (50 μL) via a syringe slowly. After gently stirring overnight, the resulting mixture was diluted with MTBE (10 mL), filtered through a Celite pad and water (5 mL). Insoluble material was filtered off, and the filtrate was washed with a mixture of MTBE and 5 N HCl (10 mL). The organic layer was further washed with water. Then, the organic layer was concentrated using a rotary evaporator to obtain pale-yellow color crude **1c** which was purified by silica gel column chromatography using ethyl acetate and hexane to obtain pure **1c** (134 mg, 56%) as an off-white semisolid. IR (KBr) ν_{max}: 2480, 1609, 1508, 1244 cm^{-1}; ^{1}H NMR (500 MHz), δ: 7.55 (s, 1H), 7.13−7.02 (m, 4H), 6.67 (d, J = 7.9 Hz, 2H), 5.21 (s, 1H), 3.90 (q, J = 7.0 Hz, 2H), 1.34 (dt, J = 6.9, 0.8 Hz, 4H). ^{13}C{^{1}H} NMR (125 MHz) δ: 157.73, 141.44, 133.63, 133.17, 130.95, 130.62, 130.46, 130.04, 120.55, 114.69, 77.38, 77.12, 76.87, 63.49, 38.30, 14.98.

■ ASSOCIATED CONTENT

ⓈI Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.3c01972.

^{1}H and ^{13}C NMR spectra of the products and HRMS data of compound **7c** (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

Masahiko Seki − *R&D Planning Department, Tokuyama Corporation, Tsukuba, Ibaraki 300-4247, Japan; Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan;* ⓞ orcid.org/0000-0002-9942-377X; Email: m.seki.tk@tokuyamagr.com

Kazushi Mashima − *Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan;* Email: mashima@phs.osaka-u.ac.jp

Authors

Sandeep Rameasharao Tapkir − *Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan*

Maheshwara Reddy Nadiveedhi − *Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan*

Shaheen Kasim Mulani − *Graduate School of Pharmaceutical Sciences, Osaka University, Suita, Osaka 565-0871, Japan*

Complete contact information is available at:
https://pubs.acs.org/10.1021/acsomega.3c01972

Notes

The authors declare no competing financial interest.

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