EurJOC
European Journal of Organic Chemistry

A Journal of
ChemPubSoc Europe

Accepted Article

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To be cited as: *Eur. J. Org. Chem.* 10.1002/ejoc.201901049

Link to VoR: http://dx.doi.org/10.1002/ejoc.201901049

Supported by
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10.1002/ejoc.201901049

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One-pot and Reducible Functional Group-Tolerated Synthesis of α-Aryl- and α-Heteroaryl-α-Trifluoromethyl Alcohols *via* Tandem Trifluoroacetylation and MPV Type Reduction

Kazumasa Funabiki,*[a] Ayaka Hayakawa,[a] Ryunosuke Kani,[a] Toshiyasu Inuzuka[b] and Yashuhiro Kubota [a]

Abstract: We have developed a new one-pot synthesis of α-aryl- and α-heteroaryl-α-trifluoromethyl alcohols carrying not only arenes with electron-withdrawing groups but also electron-deficient nitrogen-containing heteroarenes, which are of increasing interest because these compounds are some of the most important units in current fluorine-containing inhibitors or antagonists. This new method includes three tandem reactions in a one-pot synthesis: (1) the *in situ* generation of functionalized aromatic and electron-deficient heteroaromatic Grignard reagents, (2) trifluoroacetylation of the generated Grignard reagents with diphenylmethyl trifluoroacetate, and (3) successive Meerwein-Ponndorf-Verley type reduction. It offers several advantages, including no need for expensive transition metals and gaseous trifluoromethylating reagents, toleration of not only reducible functional groups on the aryl groups but also electron-deficient nitrogen-containing heterocycles, easy scalability, and the ability to suppress the formation of the bis-aldol product as a by-product by changing the ester moiety of the trifluoroacetate from an isopropyl to a diphenylmethyl group.

Introduction

Fluorine-containing organic molecules are important frameworks in functional organic molecules, medicines and pesticides.[1] Almost two decades ago, various synthetic methods for the preparation of α-*alkyl*-α-trifluoromethyl alcohols including an asymmetric version were developed, and these compounds have attracted attention as important skeletons for liquid crystal molecules.[2] As shown in Figure 1, recently, there has been increasing interest in α-*aryl*-α-trifluoromethyl alcohols, since these compounds are some of the most important units in fluorine-containing inhibitors[3] and antagonists,[4] such as LP-533401, LX1606, and LX1032. Among them, LP-533401 is a remarkable inhibitor of gut-derived serotonin (GDS) and has the potential to become a new class of bone anabolic drugs for the treatment of osteoporosis.

Therefore, it is important to develop more advanced, simple and efficient syntheses of not only α-aryl-α-trifluoromethyl alcohols carrying various substituents on the aryl group but also α-heteroaryl-α-trifluoromethyl alcohols.

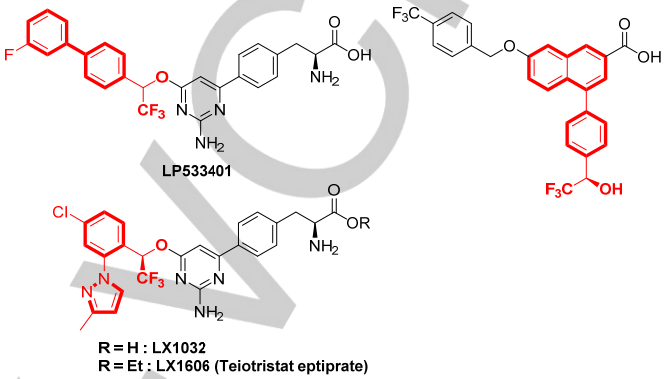
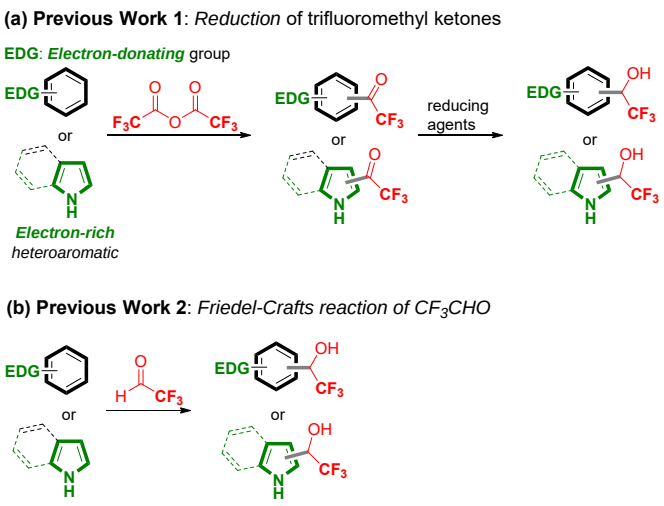


Figure 1. Recent inhibitors and antagonists carrying α-*aryl*-α-trifluoromethyl alcohol units.

Electron-donating group-substituted aryl- and electron-rich heteroaryl-α-trifluoromethyl alcohols can be synthesized by (1) reduction of aryl or heteroaryl trifluoromethyl ketones, which can be easily prepared by trifluoroacetylation of not only arenes *carrying electron-donating groups such as hydroxyl, alkoxy, and dialkylamino groups* but also *electron-rich heteroarenes, such as pyrrole and indole* in the presence of a strong Lewis acid such as $AlCl_3$, $CoCl_3$, or DMAP under a high reaction temperature (Scheme 1(a)),[5] and (2) Friedel-Crafts reaction of *electron-rich* arenes *and heteroarenes* with trifluoroacetaldehyde (Scheme 1(b))[6].



Scheme 1. Reported examples of the synthesis of α-electron-donating group-substituted aryl- and electron-rich heteroaryl-α-trifluoromethyl alcohols

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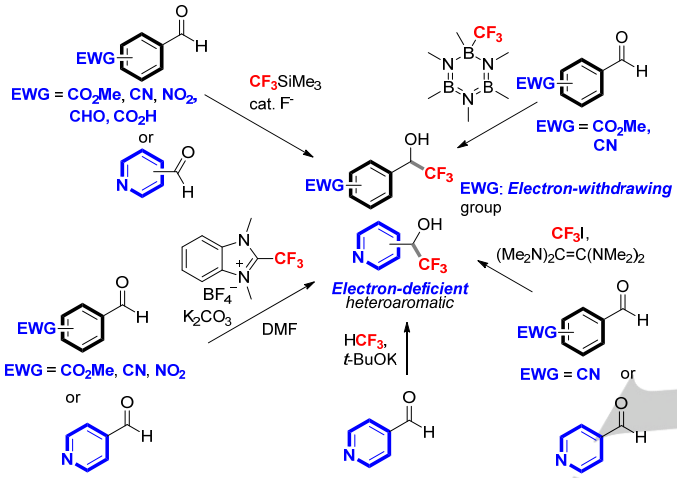
However, these methodologies are not suitable for the preparation of α-aryl-α-trifluoromethyl alcohols *carrying electron-withdrawing groups* on the phenyl ring, such as ester, cyano, and nitro groups or *α-electron-deficient heteroaryl groups*, since *trifluoroacetylation of electron-withdrawing group-substituted arenes or electron-deficient heteroarenes is quite difficult* even at a high reaction temperature and with the addition of Lewis acids. Therefore, another route that involves trifluoromethylation of the corresponding aldehydes using various nucleophilic trifluoromethylating agents, such as Ruppert-Prakash reagent,[7a-i] iodotrifluoromethane,[7j,k] trifluoromethane,[7l] borazine,[7m] and other compounds,[7n,o] has been developed for this purpose, as shown in Scheme 2.

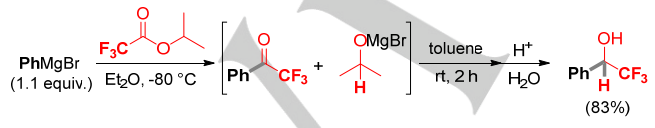
Previous Work 3: *Trifluoromethylation* of aldehydes



Scheme 2. Reported examples of the synthesis of α-electron-withdrawing group-substituted aryl- and electron-deficient heteroaryl-α-trifluoromethyl alcohols

As shown in Scheme 3, Yamazaki *et al.* reported an interesting example for the preparation of α-phenyl-α-trifluoromethyl alcohol, based on the electron-withdrawing property of fluorine atoms, by the tandem reaction of isopropyl trifluoroacetate with phenyl magnesium bromide (PhMgBr) and Meerwein-Ponndorf-Verley (MPV) type reduction of the *in situ*-generated trifluoromethyl phenyl ketone with magnesium isopropoxide.[8],[9]

Previous Work 4 : Yamazaki *et al*

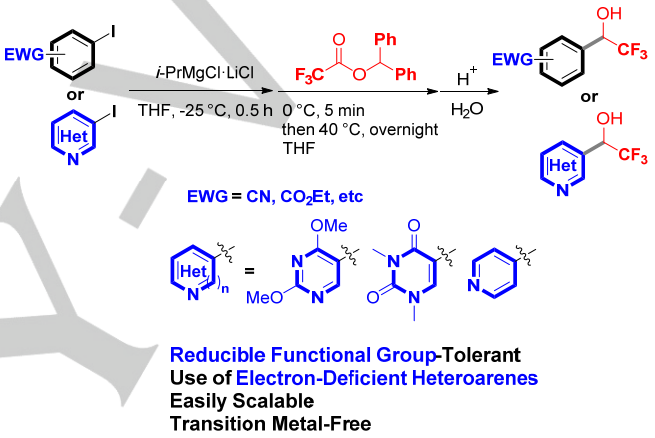


Scheme 3. Synthesis of α-phenyl-α-trifluoromethyl alcohol by the reaction of trifluoroacetic acid ester with PhMgBr and successive MPV type reduction

Although this paper has been described in detail regarding the effects of various fluoroalkyl groups compared with non-fluorinated groups, only one example of the use of Grignard reagents (PhMgBr) has been reported and there is no example of the use of aromatic Grignard reagents carrying functional groups or heteroaromatic Grignard reagents.

In this paper, we describe in detail a new one-pot synthesis of α-aryl- and α-heteroaryl-α-trifluoromethyl alcohols carrying not only arenes with electron-withdrawing groups but also electron-deficient nitrogen-containing heteroarenes, which are of increasing interest because these compounds are some of the most important units in current fluorine-containing inhibitors or antagonists. This new method includes three tandem reactions in a one-pot synthesis: (1) the *in situ* generation of functionalized aromatic and electron-deficient heteroaromatic Grignard reagents from various commercially available functionalized iodoarenes and iodoheteroarenes with a turbo Grignard reagent (*i*-PrMgCl·LiCl), [10-15] (2) trifluoroacetylation of the generated Grignard reagents with diphenylmethyl trifluoroacetate, and (3) successive Meerwein-Ponndorf-Verley type reduction, as shown in Scheme 4.

Present Work



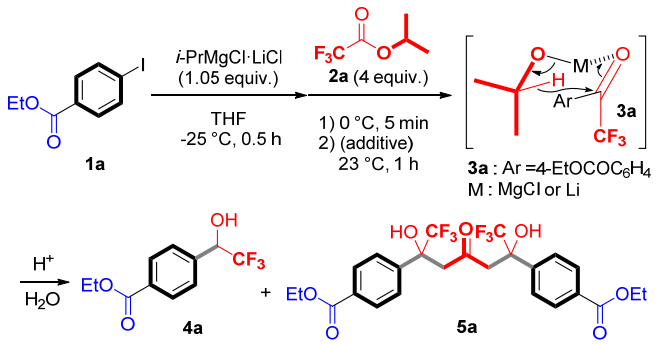
Scheme 4. Present Work

This methodology offers several advantages, such as no need for expensive transition metals and gaseous trifluoromethylating reagents, toleration of not only reducible functional groups on the aryl groups but also electron-deficient nitrogen-containing heterocycles, easy scalability, and the ability to supress the formation of the bis-aldol product as a by-product by changing the ester moiety of the trifluoroacetic acid ester from an isopropyl to a diphenylmethyl group.

Results and Discussion

The reactions of an *in situ*-generated functionalized aromatic Grignard reagent, (4-(ethoxycarbonyl)phenyl)magnesium chloride, derived from ethyl 4-iodobenzoate (**1a**) and a turbo Grignard reagent (*i*-PrMgCl·LiCl), with isopropyl trifluoroacetate (**2a**), and successive Meerwein-Ponndorf-Verley (MPV) type reduction of the *in situ*-generated trifluoromethyl ketone **3a** were examined, as shown in Table 1.

Table 1. Reactions of isopropyl trifluoroacetate (**2a**) with aromatic Grignard reagent derived from **1a** and successive MPV type reduction of *in situ*-generated trifluoromethyl ketone



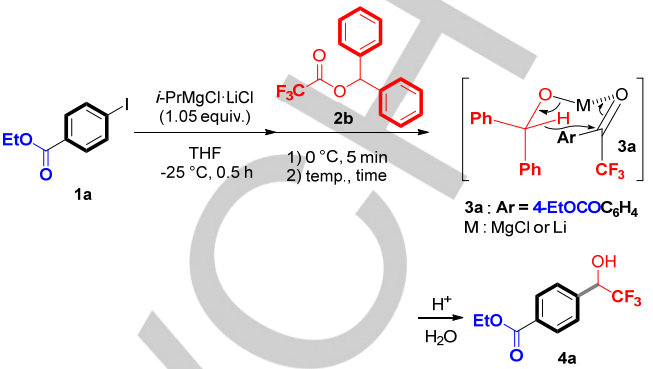
entry	additive	yield [%][a]	
1	none	**4a** (34)	**5a** (19)
2	toluene	**4a** (42)	**5a** (10)

[a] The yields stand for the yields of ^{19}F NMR.

As a result, ethyl 4-(2,2,2-trifluoro-1-hydroxyethyl)benzoate (**4a**) and bis-aldol product, diethyl 4,4'-(1,1,1,7,7,7-hexafluoro-2,6-dihydroxy-4-oxoheptane-2,6-diyl)dibenzoate (**5a**), were obtained in 34% and 19% ^{19}F NMR yields, respectively. Bis-aldol product **5a** could be produced by the reaction of *in situ*-generated trifluoromethyl ketone **3a** with acetone derived from isopropoxide. The addition of toluene (5 ml) in the MPV type reduction step not only increased α-trifluoromethylated alcohol **4a** to 42% yield but also decreased bis-aldol adduct **5a** (10%).

To prevent the formation of the bis-aldol product **5a** as a by-product, the use of diphenyl trifluoroacetate (**2b**) in place of isopropyl trifluoroacetate (**2a**) and screening of the reaction conditions were examined, as shown in Table 2. When the reaction of diphenylmethyl trifluoroacetate (**2b**) in place of isopropyl trifluoroacetate (**2a**) was carried out under the same reaction conditions, not only the alcohol **4a** but also the intermediate ketone **3a** and its equivalents were produced in 38% and 26% ^{19}F NMR yields, respectively (entry 1). Prolongation of the reaction time from 1 h to overnight improved the yield of alcohol **4a** (56%) (entry 2). When the reaction temperature was raised to 40 °C in the MPV type reduction step, reduction proceeded more efficiently and the corresponding alcohol **4a** was obtained in a yield of 71% (entry 3). MPV type reduction at reflux temperature reduced the yield (66%) of the product **4a** (entry 4). Even when the amount of diphenylmethyl trifluoroacetate (**2b**) was reduced to 3 equiv., alcohol **4a** was obtained in a similar high ^{19}F NMR and isolated yields (75%) comparable to that with 4 equiv. (entry 5). The use of 1.5 equiv. of diphenylmethyl trifluoroacetate (**2b**) at 40 °C gave a lower yield (61%) of the alcohol **4a** (entry 6).

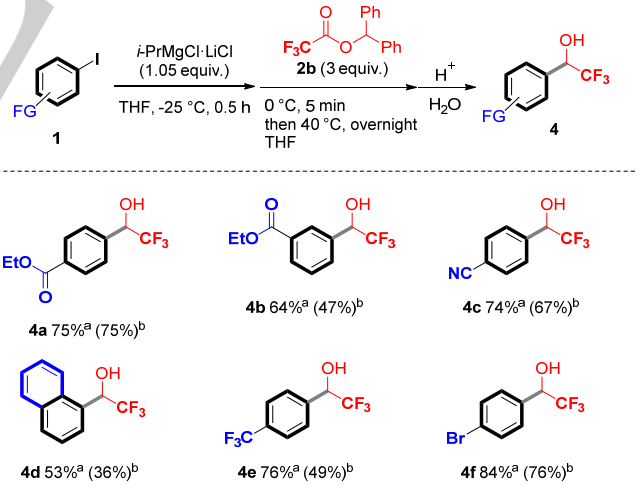
Table 2. Screening of the reaction conditions for tandem trifluoroacetylation and MPV type reduction using diphenylmethyl trifluoroacetate (**2b**)



entry	**2b** [equiv.]	temp. [°C]	time [h]	yield of **4a** [%][a]	combined yields of ketone **3a**, **3a**-hemiacetal and **3a**-hydrate [%]
1	4	23	1	38	26
2	4	23	overnight	56	0
3	4	40	overnight	71	0
4	4	reflux	overnight	66	0
5	3	40	overnight	75 (75)	0
6	1.5	40	overnight	61	0

[a] The yields stand for the yields of ^{19}F NMR. Values in parentheses stand for the yield of isolated product **4a**.

Under the optimized reaction conditions, other iodoarenes with various substituents on the benzene ring including a naphthyl group were used, as shown in Scheme 5.



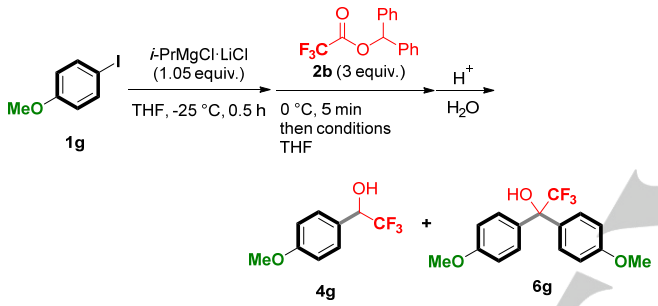
a ^{19}F NMR Yields. b Yields of isolated products.

Scheme 5. Reactions of diphenylmethyl trifluoroacetate (**2b**) with functionalized aromatic Grignard reagents and successive MPV type reduction of *in situ*-generated trifluoromethyl ketones

Thus, various iodoarenes **1** were treated with 1.05 equiv. of *i*-PrMgCl·LiCl in THF at -25 °C and 3 equiv. of diphenylmethyl trifluoroacetate (**2b**), and the resultant mixtures were heated to 40 °C and stirred overnight. As a result, iodoarenes **1** with electron-withdrawing groups, such as an ethoxycarbonyl group,

a cyano group, a bromine atom, and a trifluoromethyl group at the 3- or 4-position, also participated in the successive reaction to give the corresponding alcohols **4a,b,c,e,f** in 64-84% ^{19}F NMR yields and 47-76% isolated yields. A fuzed iodoarene such as 1-iodonaphthalene (**1d**) also reacted smoothly with the *i*-PrMgCl·LiCl complex and diphenylmethyl trifluoroacetate (**2b**) to give the corresponding ketone, followed by MPV type reduction leading to the product **4d** in moderate yield. The isolated yields of some products were lower than the ^{19}F NMR yields because some of the products are volatile due to the presence of a CF_3 group.

Although the reaction of Grignard reagent carrying a 4-methoxyphenyl group as an electron-donating group with diphenylmethyl trifluoroacetate (**2b**) also proceeded under the same reaction conditions, the corresponding alcohol **4g** and bis-Grignard reagent adduct **6g** were obtained in 22% and 31% ^{19}F NMR yields, respectively (Scheme 6). Optimization of the reaction conditions, such as increasing the amount of the ester **2b** and lowering the reaction temperature from 40 °C to 23 °C resulted in the increase of the yield of the alcohol **4g** (52% ^{19}F NMR yield and 42% isolated yield).

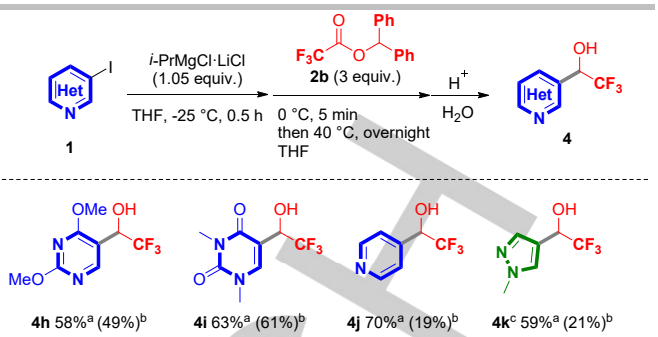


2b (equiv)	conditions	yield of **4g**	yield of **6g**
3	40 °C, overnight	22%[a] (15%)[b]	31%[a] (29%)[b]
4	23 °C, overnight	52%[a] (42%)[b]	12%[a] (trace)[b]

[a] ^{19}F NMR Yields. [b] Yields of isolated products.

Scheme 6. Reactions of diphenylmethyl trifluoroacetate (**2b**) with Grignard reagent carrying a methoxy group and successive MPV type reduction of *in situ*-generated trifluoromethyl ketone

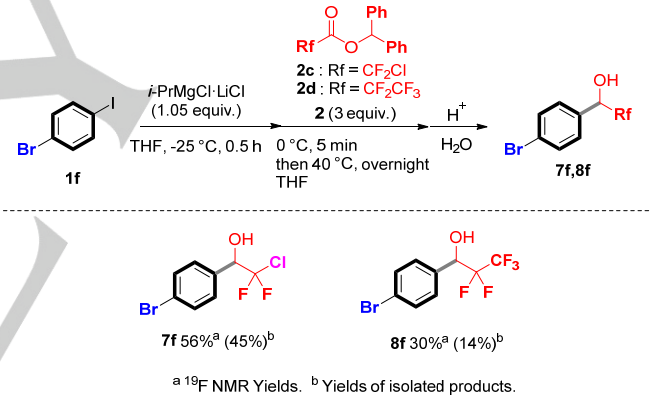
As shown in Scheme 7, the alcohols **4h,i,j** carrying pyrimidine, uracil and pyridine rings, which are electron-deficient nitrogen-containing heterocycles, were also obtained in good yields (58-70% ^{19}F NMR yields and 19-61% isolated yields) through tandem iodine-Mg exchange reaction of iodoheteroarenes, addition of the generated Grignard reagents to ester **2b** and MPV type reduction of the generated trifluorometyl ketones in a one-pot manner. In the case of Grignard reagent with an electron-donating pyrazole ring, when the reaction was performed at a lower temperature (23 °C), the corresponding alcohol **4k** was obtained in good yield (59% ^{19}F NMR yield) but low isolated yield (21%) due to its high volatility.



[a] ^{19}F NMR Yields. [b] Yields of isolated products. [c] After diphenylmethyl trifluoroacetate (4 equiv.) was added, the reaction mixture was warmed to 0 °C, 5 min. Then, the reaction mixture was stirred at 23 °C overnight.

Scheme 7. Reactions of diphenylmethyl trifluoroacetate (**2b**) with nitrogen-containing heteroaromatic Grignard reagents and successive MPV type reduction of *in situ*-generated trifluoromethyl ketones

As shown in Scheme 8, other diphenylmethyl esters **2c,d** carrying a chlorodifluoromethyl and a pentafluoroethyl group reacted with 4-bromophenylmagnesium chloride generated from 4-iodobromobenzene and *i*-PrMgCl·LiCl, to give the corresponding α-chlorodifluoro and α-pentafluoroethyl alcohols **7f,8f** in 30-56% ^{19}F NMR yields and 14-45% isolated yields.

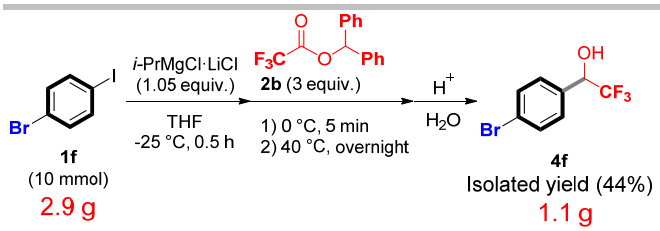


[a] ^{19}F NMR Yields. [b] Yields of isolated products.

Scheme 8. Reactions of diphenylmethyl chlorodifluoroacetate (**2c**) and pentafluoropropionate (**2d**) with Grignard reagents and successive MPV type reduction of the corresponding *in situ*-generated ketones

The yields of the products **7f,8f** are lower than that (84%) of the trifluoromethylated product **4f** due to the greater steric hindrance of the chlorodifluoromethyl and pentafluoroethyl groups than the trifluoromethyl group.[16]

Finally, gram-scale synthesis was performed, as shown in Scheme 9. The reaction proceeded even after scale-up to 10 mmol (2.9 g) to give the alcohol **4f** in an isolated yield of 44% (1.1 g).



Scheme 9. Gram-scale synthesis

Conclusions

We have developed a new one-pot synthesis of α-aryl- and α-heteroaryl-α-trifluoromethyl alcohols carrying not only arenes with the electron-withdrawing groups but also electron-deficient nitrogen-containing heteroarenes, which are of increasing interest because these compounds are some of the most important units in current fluorine-containing inhibitors or antagonists.

This new method includes three tandem reactions in a one-pot synthesis: (1) *in situ* generation of functionalized aromatic and electron-deficient heteroaromatic Grignard reagents from various commercially available functionalized iodoarenes and iodoheteroarenes with a turbo Grignard reagent, (2) trifluoroacetylation of the generated Grignard reagents with diphenylmethyl trifluoroacetate, and (3) successive Meerwein-Ponndorf-Verley type reduction. This synthesis offers several advantages, such as no need for expensive transition metals and gaseous trifluoromethylating reagents, toleration of not only reducible functional groups on the aryl groups but also electron-deficient nitrogen-containing heterocycles, easy scalability, and the ability to supress the formation of the bis-aldol product as a by-product by changing the ester moiety of the trifluoroacetic acid ester from an isopropyl to a diphenylmethyl group.

Experimental Section

Measurement. ^{1}H NMR spectra were measured at 400 MHz in deuterochloroform ($CDCl_3$) or hexadeuteroacetone (CD_3COCD_3) solutions with residual solvents as internal standards. ^{13}C NMR spectra were obtained at 100 MHz in $CDCl_3$ or CD_3COCD_3 solution with residual solvents as internal standards. ^{19}F NMR spectra were recorded at 376 MHz or 372 MHz in $CDCl_3$ or CD_3COCD_3 solutions with trichlorofluoromethane ($CFCl_3$) as an external standard.

Materials. Turbo Grignard reagent (*i*-PrMgCl·LiCl complex) was purchased from Aldrich Co. Dehydrated THF and toluene were purchased from Kanto Chemical Co. Pure products were isolated by column chromatography using silica gel (Wakogel C-200, 100-200 mesh, Wako Pure Chemical Ind., Ltd. or Silica gel 60, spherical, 40-50 μm, Kanto Chemical Co., Inc.). Analytical TLC was performed on Merck precoated (0.25 mm) silica gel 60 F_{254} plates. All chemicals were of reagent grade and, if necessary, were purified in the usual manner prior to use. Benzhydryl 2,2,2-trifluoroacetate (**2b**)[17] was prepared according to the literatures. Alcohols **4b,c,d,e,f,g,j,k**, **6g**, **7f**, and **8f** are commercially available from Aldrich Partner Products, Enamine Building Blocks, SynQuest, 1Click Chemistry Stock Products, Aurora Building Blocks, Fluorochem Product List, Boc Sciences, or UkrOrgSyntez Led.

Synthesis of Diphenylmethyl Trifluoroacetate (2b).

Diphenylmethanol (2.79 g, 15 mmol) and pyridine (3.48 g, 44.0 mmol) were dissolved in dry toluene (20 ml). After trifluoroacetic anhydride (3.83 g, 17.9 mmol) was added dropwise, the reaction mixture was warmed to 50 °C and stirred for 2 h. The reaction mixture was then cooled slowly to room temperature, water (20 ml) was added, and the mixture was stirred for 1 h. After the mixture was treated with 10% HCl aq, the aqueous phase was removed. The organic phase was then washed with water (20 ml X 2) and brine (20 ml X 1), dried over anhydrous Na_2SO_4, and concentrated under vacuum to give diphenylmethyl trifluoroacetate (**2b**) (3.862 g, 92%).

Benzhydryl 2,2,2-trifluoroacetate (2b).[17] IR (KBr) 1782 (C=O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.09 (s, 1H, CH), 7.37-7.49 (m, 10H, aryl H); ^{13}C NMR ($CDCl_3$) δ 81.1 (s), 114.8 (q, *J* = 286.3 Hz), 127.2 (s), 128.90 (s), 128.94 (s), 138.0 (s), 156.7 (q, *J* = 42.4 Hz); ^{19}F NMR ($CDCl_3$) δ –74.8 (s, 3F).

Benzhydryl 2-chloro-2,2-difluoroacetate (2c). Yield 82%; IR (KBr) 1778 (C=O) cm^{-1}; HRMS (EI) found: *m/z* 296.0406 [M]$^+$. Calcd for $C_{15}H_{11}{}^{35}ClF_2O_2$, 296.0416; ^{1}H NMR ($CDCl_3$) δ 6.97 (s, 1H, CH), 7.32-7.41 (m, 10H, aryl H); ^{13}C NMR ($CDCl_3$) δ 81.3 (s), 117.1 (t, *J* = 301.1 Hz), 127.2 (s), 128.86 (s), 128.92 (s), 138.1 (s), 158.4 (t, *J* = 34.8 Hz); ^{19}F NMR ($CDCl_3$) δ –63.8 (s, 2F).

Benzhydryl 2,2,3,3,3-pentafluoropropanoate (2d). Yield 95%; IR (KBr) 1774 (C=O) cm^{-1}; HRMS (EI) found: *m/z* 330.0661 [M]$^+$. Calcd for $C_{16}H_{11}F_5O_2$, 330.0679; ^{1}H NMR ($CDCl_3$) δ 7.02 (s, 1H, CH), 7.31-7.41 (m, 10H, aryl H); ^{13}C NMR ($CDCl_3$) δ 81.5 (s), 106.1 (tq, *J* = 263.3 Hz, 41.7 Hz), 117.9 (qt, *J* = 287.5 Hz, 68.1 Hz), 127.1 (s), 128.9 (s), 130.0 (s), 138.0 (s), 157.6 (t, *J* = 29.6 Hz); ^{19}F NMR ($CDCl_3$) δ –82.5 (s, 2F), –121.4 (s, 2F).

Typical Procedure for the Trifluoroacetylation of *In situ*-Generated Functionalized Aromatic Grignard Reagents and Successive MPV Reduction with Diphenylmethyl Trifluoroacetate (2b).

To a THF solution of *i*-PrMgCl·LiCl (1.3 M) (1.05 mmol, 0.81 ml) was added ethyl 4-iodobenzoate (**1a**) (0.283 g, 1 mmol) at –25 °C under an argon atmosphere. After the reaction mixture was stirred at that temperature for 30 min, diphenylmethyl trifluoroacetate (**2b**) (0.857 g, 3.1 mmol) was added. The resultant mixture was warmed to 0 °C and stirred for 5 min. The reaction mixture was then stirred at 40 °C overnight. The reaction mixture was quenched with NH_4Cl aq solution (20 ml), extracted with diethyl ether (30 ml X 3), dried over $NaSO_4$, and concentrated under vacuum to give a residue. After the yields were measured by ^{19}F NMR with benzotrifluoride, the residue was purified by chromatography (dichloromethane) to give ethyl 4-(2,2,2-trifluoro-1-hydroxyethyl)benzoate (**4a**) (0.187 g, 75%).

Ethyl 4-(2,2,2-trifluoro-1-hydroxyethyl)benzoate (4a). Yield 75%; R_f 0.23 (dichloromethane); mp = 74.3-74.9 ºC; IR (KBr) 1724 (C=O), 3414 (OH) cm^{-1}; HRMS (ESI) found: *m/z* 249.0735 [M+H]$^+$. Calcd for $C_{11}H_{12}F_3O_3$, 249.0739; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, *J* = 7.22 Hz, 3H, OCH_2CH_3), 4.06 (d, *J* = 4.60 Hz, 1H, OH), 4.34 (q , *J* = 7.22 Hz, 2H, OCH_2CH_3), 5.04-5.12 (m, 1H, CH), 7.53 (d , *J* = 8.30 Hz, 2H, aryl H), 8.00 (d , *J* = 8.30 Hz, 2H, aryl H); ^{13}C NMR ($CDCl_3$) δ 14.3 (s), 61.6 (s), 72.3 (q, *J* = 32.0 Hz), 124.2 (q, *J* = 283.1 Hz), 127.6 (s), 129.8 (s), 131.2 (s), 139.2 (s), 166.8 (s); ^{19}F NMR ($CDCl_3$) δ –78.0 (d, *J* = 6.8 Hz, 3F).

Diethyl 4,4'-(1,1,1,7,7,7-hexafluoro-2,6-dihydroxy-4-oxoheptane-2,6-diyl)dibenzoate (5a).[15] R_f 0.31 (hexane/ethyl acetate = 3/1); IR (KBr) 1717 (C=O), 3437 (OH) cm^{-1}; HRMS (ESI$^+$) found: *m/z* 573.1323. Calcd for $C_{25}H_{24}F_6NaO_7$: [M+Na]$^+$, 573.1324; Major isomer: ^{1}H NMR ($CDCl_3$) δ 1.38 (t, *J* = 7.18 Hz, 6H, OCH_2CH_3 X 2), 3.28 (d, *J* = 17.40 Hz, 2H, CH_AH_B X 2), 3.47 (d, *J* = 17.40 Hz, 2H, CH_AH_B X 2), 4.37 (q, *J* = 7.18 Hz, 4H, OCH_2CH_3 X 2), 4.79 (s, 2H, OH X 2), 7.54 (d, *J* = 8.55 Hz, 4H, aryl H) , 8.01 (d, *J* = 8.55 Hz, 4H, aryl H); ^{13}C NMR ($CDCl_3$) δ 14.3 (s), 47.2 (s), 61.5 (s), 76.0 (q, *J* = 29.5 Hz), 124.1 (q, *J* = 285.3 Hz), 126.34 (s), 129.77 (s), 131.19 (s), 141.2 (s), 166.15 (s), 208.3 (s); ^{19}F NMR ($CDCl_3$) δ –80.1 (s, 6F); Minor isomer: ^{1}H NMR ($CDCl_3$) δ 1.38 (t, *J* = 7.09 Hz, 6H,

OCH_2CH_3 X 2), 3.33 (d, *J* = 17.10 Hz, 2H, CH_AH_B X 2), 3.42 (d, *J* = 17.10 Hz, 2H, CH_AH_B X 2), 4.38 (q, *J* = 7.09 Hz, 4H, OCH_2CH_3 X 2), 4.83 (s, 2H, OH X 2), 7.49 (d, *J* = 8.55 Hz, 4H, aryl H) , 7.98 (d, *J* = 8.55 Hz, 4H, aryl H); ^{13}C NMR ($CDCl_3$) δ 14.3 (s), 47.1 (s), 61.5 (s), 76.0 (q, *J* = 29.5 Hz), 124.1 (q, *J* = 285.3 Hz), 126.27 (s), 129.80 (s), 131.17 (s), 141.3 (s), 166.22 (s), 208.7 (s); ^{19}F NMR ($CDCl_3$) δ –80.0 (s, 6F).

Ethyl 3-(2,2,2-trifluoro-1-hydroxyethyl)benzoate (**4b**)**.** Yield 47%; R_f 0.33 (toluene/ethyl acetate = 20/1); IR (KBr) 1701 (C=O), 3449 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.36 (t, *J* = 7.11 Hz, 3H, OCH_2CH_3), 4.10 (br s, 1H, OH), 4.34 (q , *J* = 7.11 Hz, 2H, OCH_2CH_3), 5.08 (q, *J* = 6.73 Hz, 1H, CH) , 7.44 (t , *J* = 7.68 Hz, 1H, aryl H), 7.68 (d , *J* = 7.68 Hz, 1H, aryl H), 8.01 (d , *J* = 7.68 Hz, 1H, aryl H), 8.11 (s, 1H, aryl H); ^{13}C NMR ($CDCl_3$) δ 14.2 (s), 61.6 (s), 72.3 (q, *J* = 31.9 Hz), 124.3 (q, *J* = 282.2 Hz), 128.8 (s), 130.55 (s), 130.61 (s), 132.1 (s), 135.0 (s), 166.8 (s); ^{19}F NMR ($CDCl_3$) δ –78.2 (d, *J* = 6.7 Hz, 3F).

4-(2,2,2-Trifluoro-1-hydroxyethyl)benzonitrile (**4c**)**.** Yield 67%; R_f 0.35 (hexane/ethyl acetate = 3/1); mp = 97.5-98.5 ºC; IR (KBr) 2234 (C≡N), 3379 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.36 (br s, 1H, OH), 5.00-5.23 (m, 1H, CH), 7.63 (d , *J* = 8.20 Hz, 2H, aryl H), 7.70 (d , *J* = 8.20 Hz, 2H, aryl H); ^{13}C NMR ($CDCl_3$) δ 71.9 (q, *J* = 32.3 Hz), 113.2 (s), 118.4 (s), 123.9 (q, *J* = 282.4 Hz), 128.4 (s), 132.4 (s), 139.2 (s); ^{19}F NMR ($CDCl_3$) δ –78.1 (d, *J* = 6.6 Hz, 3F).

2,2,2-Trifluoro-1-(naphthalen-1-yl)ethan-1-ol (4d). Yield = 36%; R_f 0.25 (hexane/dichloromethane = 1/1); IR (KBr) 3368 (OH) cm^{-1}, ^{1}H NMR ($CDCl_3$) δ 3.04 (d, *J* = 4.50 Hz, 1H, OH), 5.76-5.92 (m, 1H, CH), 7.45-7.63 (m, 3H, aryl H), 7.83 (d, *J* = 7.20 Hz, 1H, aryl H), 7.87-7.97 (m, 2H, aryl H), 8.03 (d, *J* = 8.00 Hz, 1H, aryl H); ^{13}C NMR ($CDCl_3$) δ 69.0 (q, *J* = 32.3 Hz), 122.9 (s) , 124.8 (q, *J* = 281.9 Hz), 125.3 (s), 125.9 (s), 126.0 (s), 126.9 (s), 129.1 (s), 130.0 (s), 130.3 (s), 131.2 (s), 133.8 (s); ^{19}F NMR ($CDCl_3$) δ –76.7 (d, *J* = 6.6 Hz,, 3F).

2,2,2-Trifluoro-1-(4-(trifluoromethyl)phenyl)ethan-1-ol (**4e**)**.** Yield 49%; R_f 0.30 (hexane/acetone = 6/1); IR (KBr) 3418 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.09 (d, *J* = 4.50 Hz,1H, OH), 5.02-5.16 (m, 1H, CH), 7.61 (d, *J* = 8.30 Hz, 2H, aryl H), 7.68 (d, *J* = 8.30 Hz, 2H, aryl H); ^{13}C NMR ($CDCl_3$) δ 72.3 (q, *J* = 32.2 Hz), 124.0 (q, *J* = 273.4 Hz), 124.1 (q, *J* = 280.9 Hz), 125.7 (q, *J* = 3.8 Hz), 131.9 (q, *J* = 32.6 Hz), 137.8 (s); ^{19}F NMR ($CDCl_3$) δ –78.3 (d , *J* = 6.7 Hz, 3F), –62.8 (s, 3F).

1-(4-Bromophenyl)-2,2,2-trifluoroethan-1-ol (**4f**). Yield 76%; R_f 0.28 (hexane/diethyl ether = 9/1); IR (KBr) 3375 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.10 (br s, 1H, OH), 4.97 (q, *J* = 6.30 Hz, 1H, CH), 7.34 (d, *J* = 8.55 Hz, 2H, aryl H), 7.54 (d, *J* = 8.55 Hz, 2H, aryl H); ^{13}C NMR ($CDCl_3$) δ 72.3 (q, *J* = 31.9 Hz), 123.9 (s), 124.1 (q, *J* = 282.2 Hz), 129.2 (s), 131.9 (s), 132.9 (s); ^{19}F NMR ($CDCl_3$) δ –78.4 (d , *J* = 6.3 Hz, 3F).

2,2,2-Trifluoro-1-(4-methoxyphenyl)ethan-1-ol (**4g**). Yield 15%; R_f 0.40 (hexane/diethyl ether = 2 /1); IR (KBr) 3426 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.74 (d, *J* = 4.00 Hz, 1H, OH), 3.82 (s, 3H, OMe), 4.89-5.03 (m, 1H, CH), 6.93 (d, *J* = 8.55 Hz, 2H, aryl H), 7.39 (d, *J* = 8.55 Hz, 2H, aryl H); ^{13}C NMR ($CDCl_3$) δ 55.4 (s), 72.5 (q, *J* = 32.2 Hz), 114.1 (s), 124.4 (q, *J* = 281.9 Hz), 126.3 (s), 128.9 (s), 160.5 (s); ^{19}F NMR ($CDCl_3$) δ –78.4 (d, *J* = 7.6 Hz, 3F).

2,2,2-trifluoro-1,1-bis(4-methoxyphenyl)ethan-1-ol (**6g**). Yield 29%; R_f 0.18 (hexane/dichloromethane = 1/2); IR (KBr) 3445 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.10 (br s, 1H, OH), 3.80 (s, 6H, OMe), 6.87 (d, *J* = 9.00 Hz, 4H, aryl H), 7.41 (d, *J* = 9.00 Hz, 4H, aryl H); ^{13}C NMR ($CDCl_3$) δ 55.3 (s), 79.0 (q, *J* = 29.1 Hz), 113.6 (s), 125.6 (q, *J* = 286.6 Hz), 128.9 (s), 131.9 (s), 159.6 (s); ^{19}F NMR ($CDCl_3$) δ –74.5 (s, 3F).

1-(2,4-Dimethoxypyrimidin-5-yl)-2,2,2-trifluoroethan-1-ol (**4h**). Yield 49%; R_f 0.35 (hexane/ethyl acetate = 3 /1); mp = 142.0-142.6 ºC; IR (KBr) 1721 (C=N), 3503 (OH) cm^{-1}; HRMS (ESI) found: *m/z* 261.0464 [M+Na]$^+$. Calcd for $C_8H_9F_3N_2O_3Na$, 261.0463; ^{1}H NMR ($(CD_3)_2CO$) δ 3.96 (s, 3H, OCH_3), 4.00 (s, 3H, OCH_3), 5.34-5.45 (m, 1H, OH), 6.04 (d, *J* = 5.90 Hz, 1H, CH), 8.47 (s, 1H, aryl H); ^{13}C NMR ($(CD_3)_2CO$) δ 54.6 (s), 55.2 (s), 65.2 (q, *J* = 32.9 Hz), 110.5 (s), 125.8 (q, *J* = 281.8 Hz), 159.1 (s), 166.5 (s), 169.3 (s); ^{19}F NMR ($(CD_3)_2CO$) δ –79.2 (d, *J* = 5.9 Hz, 3F).

1,3-Dimethyl-5-(2,2,2-trifluoro-1-hydroxyethyl)pyrimidine-2,4(1*H*,3*H*)-dione (**4i**). Yield 61%; R_f 0.43 (hexane/ethyl acetate = 1/2); mp = 143.8-144.8 ºC; IR (KBr) 1667 (C=C), 1724 (C=O), 3526 (OH) cm^{-1}; HRMS (ESI) found: *m/z* 261.0448 [M+Na]$^+$. Calcd for $C_8H_9F_3N_2O_3Na$, 261.0463; ^{1}H NMR ($(CD_3)_2CO$) δ 3.25 (s, 3H, CH_3), 3.48 (s, 3H, CH_3), 5.16-5.24 (m, 1H, OH), 5.85 (d, *J* = 6.30 Hz, 1H, CH), 7.78 (s, 1H, aryl H); ^{13}C NMR ($(CD_3)_2CO$) δ 27.9 (s), 37.3 (s), 65.9 (q, *J* = 32.6 Hz), 107.5 (s), 125.8 (q, *J* = 281.9 Hz), 145.0 (s), 152.0 (s), 163.0 (s); ^{19}F NMR ($(CD_3)_2CO$) δ –79.4 (d, *J* = 6.3 Hz, 3F).

2,2,2-Trifluoro-1-(pyridin-4-yl)ethan-1-ol (4j). Yield = 19%; R_f 0.23 (hexane/ethyl acetate = 2/1); IR (KBr) 3156 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 5.09 (q, *J* = 6.60 Hz, 1H, CH), 6.47 (br s, 1H, OH), 7.54 (d, *J* = 4.55 Hz, 2H, aryl H), 8.55 (d, *J* = 4.55 Hz, 2H, aryl H); ^{13}C NMR ($CDCl_3$) δ 71.1 (q, *J* = 31.9 Hz), 122.7 (s), 124.1 (q, *J* = 284.8 Hz), 145.5 (s), 148.8 (s); ^{19}F NMR ($CDCl_3$) δ –77.7 (s, d, *J* = 6.6 Hz, 3F).

2,2,2-Trifluoro-1-(1-methyl-1*H*-pyrazol-3-yl)ethan-1-ol (**4k**). Yield 21%; R_f 0.34 (hexane/ethyl acetate = 1/1); IR (KBr) 1724 (C=N), 3603 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.86 (s, 3H, CH_3), 5.00 (q, *J* = 6.73 Hz, 1H, CH), 7.466 (s, 1H, aryl H) , 7.471 (s, 1H, aryl H), Signal derived from OH were not able to be assigned; ^{13}C NMR ($CDCl_3$) δ 39.1 (s), 66.0 (q, *J* = 33.6 Hz), 116.1 (s), 124.6 (q, *J* = 281.8 Hz), 129.7 (s), 138.3 (s); ^{19}F NMR ($CDCl_3$) δ –79.1 (d, *J* = 6.7 Hz, 3F).

1-(4-Bromophenyl)-2-chloro-2,2-difluoroethan-1-ol (**7f**). Yield 45%; R_f 0.20 (hexane/dichloromethane = 1/1); IR (KBr) 3414 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.91 (d, *J* = 3.57 Hz, 1H, OH), 4.99-5.06 (m, 1H, CH), 7.36 (d, *J* = 8.07 Hz, 2H, aryl H), 7.54 (d, *J* = 8.50 Hz, 2H, aryl H); ^{13}C NMR ($CDCl_3$) δ 76.8 (t, *J* = 27.7 Hz), 123.9 (s), 128.7 (t, *J* = 296.9 Hz), 129.6 (s), 131.7 (s), 133.2 (s) ; ^{19}F NMR ($CDCl_3$) δ –63.0 (dd, *J* = 165.8 Hz, 7.1 Hz, F), –64.9 (dd, *J* = 165.8 Hz, 8.5 Hz, F).

1-(4-Bromophenyl)-2,2,3,3,3-pentafluoropropan-1-ol (**8f**). Yield 14%; R_f 0.28 (hexane/dichloromethane = 1/1); IR (KBr) 3406 (OH) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.61 (d, *J* = 4.94 Hz, 1H, OH), 5.08-5.12 (m, 1H, CH), 7.34 (d, *J* = 8.07 Hz, 2H, aryl H), 7.56 (d, *J* = 8.50 Hz, 2H, aryl H); ^{13}C NMR ($CDCl_3$) δ 71.6 (dd, *J* = 27.7 Hz, 23.0 Hz), 112.9 (ddq, *J* = 261.6 Hz, 255.5 Hz, 35.5 Hz), 119.1 (qt, *J* = 287.5 Hz, 70.9 Hz), 124.1 (s), 129.6 (s), 132.0 (s), 132.9 (s); ^{19}F NMR ($CDCl_3$) δ –81.0 (s, 3F), –121.7 (dd, *J* = 276.1 Hz, 7.6 Hz, F), –129.1 (dd, *J* = 276.1 Hz, 16.2 Hz, F).

Acknowledgements

We thank Mr. Sawada for measuring HRMS of the products. .

Conflict of interest

The authors declare no conflict of interest.

Keywords: trifluoromethyl • alcohols• turbo Grignard reagent • Meerwein-Ponndorf-Verley type reduction • nitrogen-containing heterocycles

[1] For recent reviews, see. (a) V. Gouverneur, K. Seppelt, Eds, *Chem. Rev.* **2015**, *115*, 566-1306. (b) E. P. Gillis, K. J. Eastman, M. D. Hill, D. J. Donnelly, N. A. Meanwell, *J. Med. Chem.* **2015** *58*, 218315-218359. (c) V. Gouverneur and K. Müller, Eds., *Fluorine in Pharmaceutical and*

Medicinal Chemistry: From Biophysical Aspects to Clinial Applications, **2012**, Word Scientific Publishing Co. Pte. Ltd. (d) R. Berger, G. Resnati, P. Metrangolo, E. Weberd and J. Hulliger, *Chem. Soc. Rev.* **2011**, *40*, 3496-3508.

[2] For examples, see. (a) Y. Takanishi, H. Takezoe,; Y. Suzuki, I. Kobayashi, T. Yajima, M. Terada, K. Mikami, *Angew. Chem. Int. Ed.* **1999**, *38*, 2354-2356. (b) K. Mikami, T. Yajima, M. Terada, Y. Suzuki, I. Kobayashi, *Chem. Commun.* **1997**, 57-58

[3] (a) K. A. Lyseng-Williamson, *Drugs* **2018**, *78*, 941-950. (b) D. Pawlak, B. Znorko, B. Kalaska, T. Domaniewski, R. Zawadzki, P. Lipowicz, M. Doroszko, U, Łebkowska, P. Grabowski, K. Pawlak, *Bone* **2018**, *113*, 124-136. (c) G. M. G. Lima B. J. M. Corazza R. M. Moraes F. E. de Oliveira L. D. de Oliveira G. C. N. Franco D. S. Perrien F. Elefteriou A. L. Anbinder, *J. Periodontal Res.* **2016**, *51*, 661-668. (d) D. R. Goldberg, S. De Lombaert, R. Aiello, P. Bourassa, N. Barucci, Q. Zhang, V. Paralkar, J. Valentine, W. Zavadoski, *Bioorg. Med. Chem. Lett.* **2016**, *26*, 1124-1129. (e) C. -M. Oh, J. Namkung, Y. Go, K. E. Shong, K. Kim, H. Kim, B. -Y. Park, H. W. Lee, Y. H. Jeon, J. Song, M. Shong, V. K. Yadav, G. Karsenty, S. Kajimura, I. -K. Lee, S. Park, H. Kim, *Nat. Commun.* **2015**, *6*, 6794. (f) J. J. Kim, H. Wang, J. D. Terc, B. Zambrowicz, Q. M. Yang, W. I. Khan, *Am. J. Physiol.* **2015**, *309*, G455–G465. (g) V. Yadav, S. Balaji, P. S. Suresh, X. S. Liu, X. Lu, Z. Li, X. E. Guo, J. J. Mann, Anil. K. Balapure, M. D. Gershon, R. Medhamurthy, M. Vidal, G. Karsenty, P. Ducy, *Nat. Med.* **2010**, *16*, 308-312. (h) K. G. Margolis, K. Stevanovic, Z. Li, Q. M. Yang, T. Oravecz, B. Zambrowicz, K. G. Jhaver, A. Diacou, M. D. Gershon, *Gut* **2014**, *63*, 928-937.

[4] J. Y. Gauthier, M. Belley, D. Deschenes, J. -F. Fournier, S. Gagne, Y. Gareau, M. Hamel, M. Henault, H. Hyjazie, S. Kargman, G. Lavallee, J. -F. Levesque, L. Li, Y. Mamane, J. Mancini, N. Morin, E. Mulrooney, J. Robichaud, M. Therien, G. Tranmer, Z. Wang, J. Wu, W. C. Black, *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2836-2839.

[5] (a) J. Margalef, T. Slagbrand, F. Tinnis, H. Adolfsson, M. Dieguez, O. Pamies, *Adv. Synth. Catal.* **2016**, *358*, 4006-4018. (b) Y. Harauchi, C. Takakura, T. Furumoto, R. C. Yanagita, Y. Kawanami, *Tetrahedron: Asymmetry* **2015**, *26*, 333-337. (c) D. V. Yarmoliuk, V. V. Arkhipov, M. V. Stambirskyi, Y. V. Dmytriv, O. V. Shishkin, A. A. Tolmachev and P. K. Mykhailiuk, *Synthesis* **2014**, *46*, 1254-1260. (d) L. Mitchell, P. Williamson, B. Ehrlichova, A. E. Anderson, V. R. Seymour, S. E. Ashbrook, N. Acerbi, L. M. Daniels, R. I. Walton, M. L. Clarke, P. A. Wright, *Chem. Eur. J.* **2014**, *20*, 17185-17197. (e) B. Raimer and T. Lindel, *Chem. Eur. J.* **2013**, *19*, 6551-6555. (f) S. S. Ribeiro, C. Raminelli and A. L. M. Porto, *J. Fluorine Chem*. **2013**, *154*, 53-59. (g) H. Zhao, B. Qin, X. Liu and X. Feng, *Tetrahedron* **2007**, *63*, 12731-12734. (h) A. D. Allen, R. Girdhar, M. P. Jansen, J. D. Mayo and T. T. Tidwell, *J. Org. Chem.* **1986**, *51*, 1324-1331.

[6] (a) L. Mitchell, P. Williamson, B. Ehrlichova, A. E. Anderson, V. R. Seymour, S. E. Ashbrook, N. Acerbi, L. M. Daniels, R. I. Walton, M. L. Clarke, P. A. Wright, *Chem. Eur. J.* **2014**, *20*, 17185-17197. (b) S. M. Landge, D. A. Borkin, B. Török, *Tetrahedron Lett.* **2007**, *48*, 6372-6376. (c) Y. Gong, K. Kato, H. Kimoto, *Bull. Chem. Soc. Jpn.* **2000**, *73*, 249-250. (d) A. Ishii, A. V. Soloshonok, K. Mikami, *J. Org. Chem.* **2000**, *65*, 1597-1600.

[7] With $TMSCF_3$: (a) D. X. Ngo, W. W. Kramer, B. J. McNicholas, H. B. Gray, B. J. Brennan, *Inorg. Chem.* **2019**, *58*, 737–746. (b) K. Mishra, K. C. Bharadwaj, R. M. Singh, *Tetrahedron Lett.* **2018**, *59*, 3439-3442. (c) V. A. Pistritto, J. M. Paolillo, K. A. Bisset, N. E. Leadbeater, *Org. Biomol. Chem.* **2018**, *16*, 4715-4719; (d) S. Okusu, K. Hirano, Y. Yasuda, E. Tokunaga, N. Shibata, *RSC Adv.* **2016**, *86*, 82716-82720. (e) J. Sun, X. Peng, H. Guo, *Tetrahedron Lett.* **2015**, *56*, 797-800. (f) H. Cheng, Y. Pei, F. Leng, J. Li, A. Liang, D. Zou, Y. Wu, Y. Wu, *Tetrahedron Lett.* **2013**, *54*, 4483-4486. (g) C. B. Kelly, M. A. Mercadante, T. A. Hamlin, M. H. Fletcher, N. E. Leadbeater, *J. Org. Chem.* **2012**, *77*, 8131-8141. (h) M. Baumann, I. R. Baxendale, L. J. Martin, S. V. Ley, *Tetrahedron* **2009**, *65*, 6611-6625. (i) J. J. Song, Z. Tan, J. T. Reeves, F. Gallou, N. K. Yee, C. H. Senanayake, *Org. Lett.* **2005**, *7*, 2193-2193. With CF_3I: (j) S. Aït-Mohand, N. Takechi, M. Médebielle, W. R. Dolbier, Jr., *Org. Lett.* **2001**, *3*, 4271-4273. (k) K. Aikawa, W. Toya, Y. Nakamura, K. Mikami, *Org. Lett.* **2015**, *17*, 4996-4999. With HCF_3: (l) B. Musio, E. Gala, S. V. Ley, *ACS Sustainable Chem. Eng.* **2018**, 6, 1489–1495. With borazine: (m) J. B. Geri, M. M. W. Wade, N. K. Szymczak, *Angew. Chem. Int. Ed.* **2018**, *57*, 1381-1385. With benzimidazolium salts: (n) K. Kawazoe, K. Yoshioka, *PCT Int. Appl.* 2015199109. With $CF_3S(O)NR^1R^2$, see: (o) D. Inschauspe, J. -B. Sortais, T. Billard, B. R. Langlois, *Synlett* **2003**, 233-235.

[8] T. Yamazaki, T. Terajima, T. Kawasaki, *Tetrahedron* **2008**, *64*, 2419-2424.

[9] For Meerwein-Ponndorf-Verley (MPV) type reduction including asymmetric version of trifluoromethyl ketones, see. (a) H. Huang, H. Zong, G. Bian, L. Song, *J. Org. Chem.* **2015**, *80*, 12614–12619. (b) K. Funabiki, H. Iwata, Y. Yano, Y. Kubota, M. Matsui, *Org. Chem. Front.* **2015**, *2*, 369-371. (c) M. Calvillo-Barahona, C. Cordovilla, M. N. Genov, J. M. Martinez-Ilarduya, P. Espinet, *Dalton Trans.* **2013**, *42*, 14576-14582. (d) K. Mikami, T. Murase, Y. Itoh, *J. Am. Chem. Soc.* **2007**, *129*, 11686-11687. (e) Y. S. Sokeirik, K. Sato, M. Omote, A. Ando, I. Kumadaki, *Tetrahedron Lett.* **2006**, *47*, 2821-2824. (f) Y. S. Sokeirik, K. Sato, A. Ando, I. Kumadaki, *J. Fluorine Chem.* **2006**, *127*, 150-152. (g) S. Sasaki, T. Yamauchi, H. Kubo, M. Kanai, A. Ishii, K. Higashiyama, *Tetrahedron Lett.* **2005**, *46*, 1497-1500. (h) K. H. Yong, J. M. Chong, *Org. Lett.* **2002**, *4*, 4139-4142. (i) S. A. Lermontov, S. V. Shkavrov, N. V. Kuryleva, *J. Fluorine Chem.* **2003**, *121*, 223-225. (j) D. Nasipuri, P. K. Bhattacharya, *J. Chem. Soc., Perkin Trans. 1* **1977**, 576-578. (k) J. D. Morrison, R. W. Ridgway, *J. Org. Chem.* **1974**, *39*, 3107-3110.

[10] For recent reviews of turbo Grignard reagent, see. (a) P. Knochel, W. Dohle, N. Gommermann, F. F. Kneisel, F. Kopp, T. Korn, I. Sapountzis, V. A. Vu, *Angew. Chem. Int. Ed.* **2003**, *42*, 4302-4320. (b) R. L. -Y. Bao, R. Zhao, L. Shi, *Chem. Commun.* **2015**, *51*, 9744-9744.

[11] For fluorination, see. (a) S. Yamada, A. Gavryushin, P. Knochel, *Angew. Chem. Int. Ed.* **2010**, *49*, 2215-2218. (b) P. Anbarasan, H. Neumann, M. Beller, *Angew. Chem. Int. Ed.* **2010**, *49*, 2219-2222.

[12] For fluoroalkylation, see. M. Shiosaki, M. Inoue, *Tetrahedron Lett.* **2014**, *55*, 6839-6843.

[13] For trifluoromethylthiolation, see. F. Baert, J. Colomb, T. Billard, *Angew. Chem. Int. Ed.* **2012**, *51*, 10382-10385.

[14] For other example with trifluoromethyl phenyl ketone, see. J. T. Kuethe, K. M. Maloney, *Tetrahedron* **2013**, *69*, 5248-5258.

[15] For trifluoroacetylation, see. K. Funabiki, A. Hayakawa, T. Inuzuka, *Org. Biomol. Chem.* **2018**, *18*, 913-918.

[16] K. W. Tafts Jr, *Steric Effects in Organic Chemistry*, Newman, M. S.; Ed, John Wiley & Suns, New York, **1956**, p. 556.

[17] B. Denegri, O. Kronja, *J. Org. Chem*. **2009**, *74*, 5927-5933.

10.1002/ejoc.201901049

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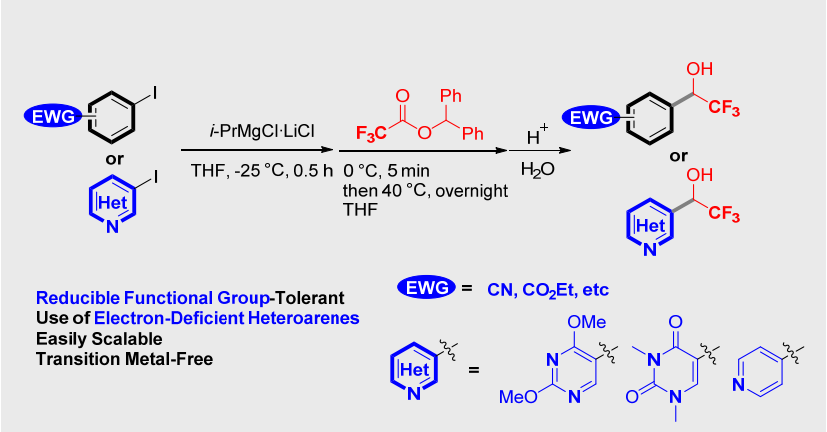

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One-pot and Reducible Functional Group-Tolerated Synthesis of α-Aryl and α-Heteroaryl α-Trifluoromethyl Alcohols via Tandem Trifluoroacetylation and MPV Type Reduction

Tandem Reaction:

Tandem reaction, such as (1) the *in situ* generation of functionalized aromatic and electron-deficient heteroaromatic Grignard reagents, (2) trifluoroacetylation with diphenylmethyl trifluoroacetate, and (3) successive Meerwein-Ponndorf-Verley type reduction giving α-aryl- and α-heteroaryl-α-trifluoromethyl alcohols is reported.