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This article is dedicated to Professor Satoshi Ōmura in celebration of his 2015 Nobel Prize.

Regular Article

Enhanced Structural Variety of Nonplanar *N*-Oxyl Radical Catalysts and Their Application to the Aerobic Oxidation of Benzylic C–H Bonds

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The design and synthesis of structurally variable, nonplanar *N*-oxyl radical catalysts and their application to the aerobic oxidation, etherification, and acetoamidation of benzylic C–H bonds are described. The catalytic oxidation of C–H bonds represents a powerful tool to synthesize oxygenated functional molecules from simple hydrocarbons in a straightforward way. Electron-deficient *N*-oxyl radical catalysts, such as phthalimidoyl *N*-oxyl (PINO) radical, generated from *N*-hydroxyphthalimide (1), have attracted much attention because of their applications in the oxidation of C–H bonds with high bond dissociation energy (BDE). However, a few sites in 1 are available for structural modifications and improvements of the catalytic performance. By replacing one carbonyl group in 1 with a trifluoromethyl (CF_3)-substituted sp^3-carbon, we generated an additional tunable site and a nonplanar backbone, while retaining the desirable electron-withdrawing properties and increasing the lipophilicity with respect to 1. We synthesized a variety of *N*-hydroxy precatalysts containing such a CF_3 moiety, and investigated their utility in the aerobic oxidation of benzylic C–H bonds. Precatalysts with electron-withdrawing substituents, such as trifluoroethoxy and the acetophenone moieties, afforded higher yields than a corresponding methoxy-substituted analogue. The introduction of substituents at the aromatic ring was also effective, as evident from the performance of 7-CF_3 and 4,5,6,7-tetrafluoro precatalysts. Especially the combination of trifluoroethoxy- and 4,5,6,7-tetrafluoro substitution afforded a superior performance. These catalyst systems exhibited high functional group tolerance during the aerobic oxidation of C–H bonds, and benzylic etherification and Ritter-type reactions could be carried out at room temperature when a selected precatalyst and *N*-bromosuccinimide (NBS) were used.

Key words *N*-oxyl radical; aerobic oxidation; organocatalyst; C–H oxidation

The catalytic oxidation of C–H bonds is a valuable transformation in organic chemistry that leads to medicinally attractive oxygenated functional molecules in a small number of synthetic steps.[1–3] In the context of green chemistry, the use of molecular oxygen (O_2) for this conversion has recently attracted much attention, as it minimizes both the use of potentially hazardous oxidants and the generation of byproducts. However, C–H oxidations using O_2 are challenging, as the formation of reactive oxygen species from triplet O_2 is kinetically unfavorable. Therefore, bespoke initiators/catalysts that activate C–H bonds and/or O_2 are required, in order to perform aerobic C–H oxidations efficiently.[3,4]

Electron-deficient *N*-oxyl radicals, which are generated from the oxidation of *N*-hydroxy compounds, have been used to homolytically cleave the inert C(sp^3)–H bonds of alkanes. The phthalimidoyl *N*-oxyl (PINO) radical, derived from *N*-hydroxyphthalimide (**1**), is a representative example that has been applied to various aerobic or non-aerobic C–H oxidations.[5–7] However, **1** suffers from serious limitations in such reactions, *e.g.* poor solubility in common organic solvents and rapid autodecomposition.[8,9]

Introducing substituents at the aromatic ring of **1** has been reported to enhance its solubility and stability (Fig. 1). Thus, the group of Ishii was able to develop a lipophilic derivative of **1** (**A**), which is soluble in alkanes,[10] as well as derivatives **B** and **C**, which contain long fluorinated alkyl chains and are thus soluble in trifluorotoluene.[11] The group of Einhorn synthesized tetraphenyl- (**D**)[12] and silyl-substituted[13] (**E**) analogues with enhanced stability, and the group of Xu reported the synthesis of tetrahalogenated derivatives of **1**, whereby tetrachloro analogue **F** showed the best catalytic performance.[14] Nevertheless, the backbone of **1** remains characterized by its inherent planarity and its limited number of modification sites, which restrict a further improvement of the catalytic performance and the introduction of additional functional groups.

Herein, we report an unprecedented approach towards nonplanar, electron-deficient *N*-oxyl radicals, containing an additional tunable site, which provides these compounds with enhanced solubility, stability, and structural diversity. We furthermore explored the utility of these compounds in the catalytic oxidation, etherification, and acetoamidation of benzylic C(sp^3)–H bonds.

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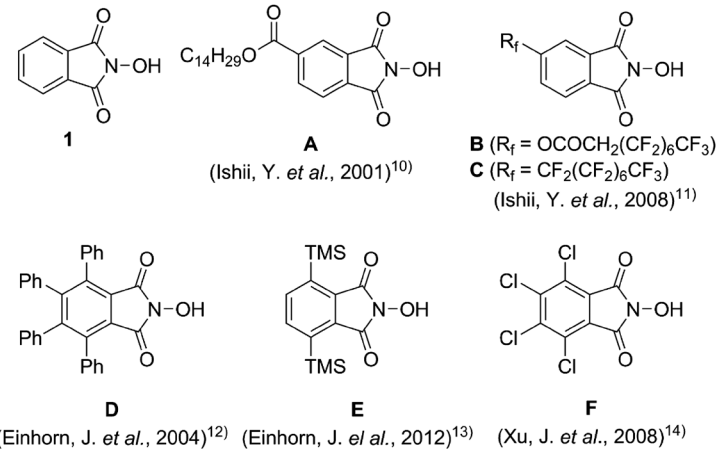


Fig. 1. Chemical Structure of **1** and Previously Reported Derivatives

Results and Discussion

Structural Design of a Nonplanar, CF_3-Substituted *N*-Oxyl Radical Precursor

The high bond dissociation energy (BDE) of the NO–H bond in **1** (88.1 kcal/mol in *t*-BuOH), which is sufficient for cleaving benzylic, tertiary, and even secondary C(sp^3)–H bonds, is due to the presence of two carbonyl groups adjacent to the *N*-OH moiety. These electron-withdrawing groups destabilize the resulting oxyl radical by rendering the delocalization of the nitrogen-lone pair inefficient therein.[15]

Due to the structural simplicity of **1**, modifiable sites are limited, except for those of the aromatic ring. To overcome this limitation, we envisaged that the transformation of one carbonyl group into an sp^3 carbon should provide a feasible route to an additional tunable site in close proximity to the *N*-hydroxy moiety, which would simultaneously afford a nonplanar structure. This strategy should allow access to unprecedented structural tuning in order to improve catalytic performance, even though the elimination of a carbonyl group should lower the BDE.

The substitution of the carbonyl group at the R^5 position in **1** with the lipophilic and electron-withdrawing trifluoromethyl (CF_3) group should not only counterbalance such a decreased BDE, but also enhance the solubility of the resulting derivative.[16] Simultaneous modifications of the aromatic substituents (R^1–R^4) should further improve these properties (Fig. 2).

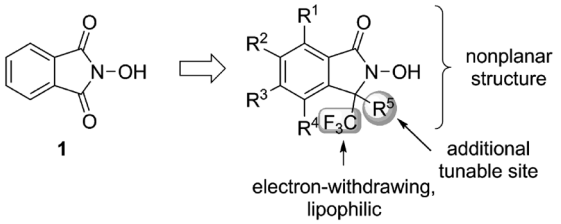


Fig. 2. Structural Design of a Novel *N*-Oxyl Radical Precursor Based on **1**

Preparation of *N*-Hydroxy Precatalysts

N-Hydroxy precatalysts **5**, **6**, and **9** were synthesized from **1** in five steps (Chart 1). Initially, **1** was converted into intermediate **2** in three steps, following our previously reported procedure.[16] Then, the chloro group of **2** was substituted with methoxy, 2,2,2-trifluoroethoxy, or acetophenone moieties under silver-mediated S_N1 conditions, using the corresponding alcohols or a silyl enol ether (**7**). The ensuing removal of the protecting benzyl group under hydrogenolysis conditions afforded *N*-hydroxy precatalysts **5**, **6**, and **9**.

We also synthesized *N*-oxyl radical precursors containing a CF_3 group at position 7 of the aromatic ring (**20** and **21**; Chart 2). For this purpose, commercially available 3-nitrophthalic anhydride (**10**) was reacted with $H_2NOBn \cdot HCl$ to afford **11**, whose nitro group was reduced with iron powder to yield amine **12**. Subsequently, **12** was converted into iodide **13** by a Sandmeyer reaction, and an ensuing Ruppert–Prakash trifluoromethylation[17] afforded the 7- and 4-iodo isomers **14a** (46%) and **b** (36%), which were separated after trituration with Et_2O and column chromatography.[18] Treatment of alcohol **14a** with methanesulfonyl chloride (MsCl) furnished chloride **15**, whose chloro group was removed by reaction with methanol or 2,2,2-trifluoroethanol (TFE) to afford ethers **16** and **17**, respectively. The iodo group of these compounds was substituted with a CF_3 group using $(Ph_3P)_3CuCF_3$,[19] and deprotection eventually afforded CF_3-substituted *N*-hydroxy precatalysts **20** and **21**.

Acetophenone-substituted 7-trifluoromethyl analogue **28** was prepared following a similar synthetic route, starting from **22**.[20] As the removal of the benzyl group was unsuccessful in this case, the *p*-methoxybenzyl (PMB) group was selected as a protecting group for the *N*-hydroxy moiety (Chart 3). The PMB group could be removed successfully in the last step under trifluoroacetic acid (TFA)/C_6Me_5H conditions[16,21] to afford **28**.

Next, we tackled the synthesis of tetrafluoro analogues **34** and **35**, starting from **29**, *i.e.*, the 4,5,6,7-tetrafluoro derivative of **1**[22] as shown in Chart 4. As expected, protection of the *N*-hydroxy moiety in **29** as a PMBether, followed by nucleophilic trifluoromethylation successfully furnished alcohol **31**. However, our general protocol (Chart 1), consisting of chlorination (Et_3N–MsCl) followed by silver-mediated S_N1 substitution,[16] did not afford **32** or **33** from **30**, most likely on account of the low reactivity of the chlorinated intermediate towards the silver salt. As an alternative, we chose to carry out a one-pot mesylation-substitution reaction. After **31** was mesylated using Ms_2O–Et_3N at −78°C, methanol or TFE was added to the mixture, which was then warmed to room temperature. This protocol successfully furnished ethers **32** and **33**, and

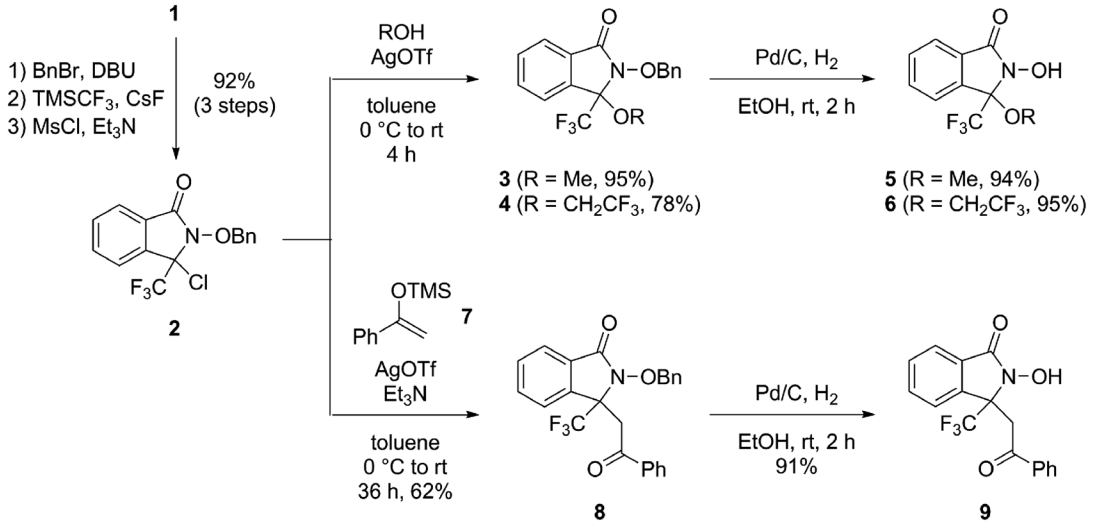


Chart 1. Preparation of *N*-Hydroxy Precatalysts **5**, **6**, and **9**

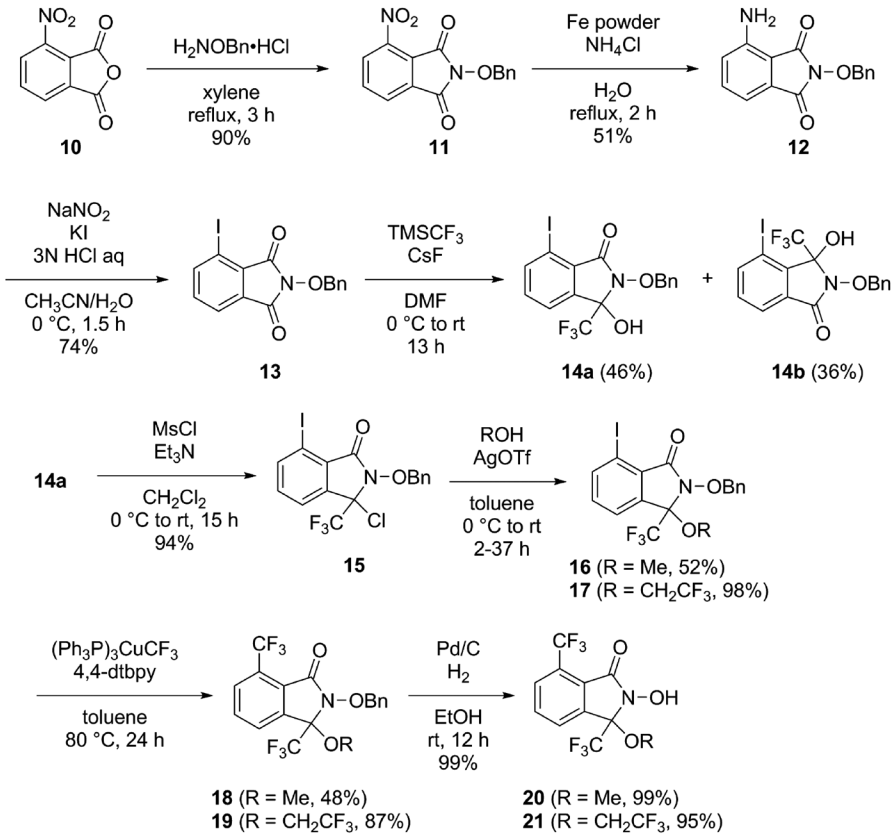


Chart 2. Preparation of 7-Trifluoromethyl *N*-Hydroxy Precatalysts **20** and **21**

their PMB groups could be removed with TFA–C_6Me_5H to afford 4,5,6,7-tetrafluoro *N*-hydroxy precatalysts **34** and **35**. Unfortunately, an acetophenone-substituted analogue could not be synthesized, presumably due to the low reactivity of the silyl enol ether towards the mesylated or chlorinated intermediates.

Aerobic Oxidation of Benzylic C–H Bonds with *N*-Oxyl Radical Catalysts

As a part of our ongoing research program directed towards *N*-oxyl radical-catalyzed aerobic oxidations,[23–25] we applied the newly synthesized *N*-hydroxy precatalysts to the aerobic oxidation of benzylic C–H bonds. The results obtained are summarized in Table 1.

The oxygenation of the benzylic C–H bonds in **36a** was investigated using 5 mol% of the *N*-hydroxy precatalyst, 1 mol% of $Co(OAc)_2$, and 1 mol% of $Mn(OAc)_3 \cdot 2H_2O$ in CH_3CN under an atmosphere of O_2 (1 atm) at 60°C. When **1** was used as a control catalyst, ketone **37a** was obtained in 92% yield after 12 h (entry 1). Precatalyst **5**, containing a CF_3 and a methoxy substituent instead of a carbonyl group, afforded **37a** in lower yield (23%, entry 2). We found that substituting the methoxy group with more electron-deficient 2,2,2-trifluoroethoxy (**6**)

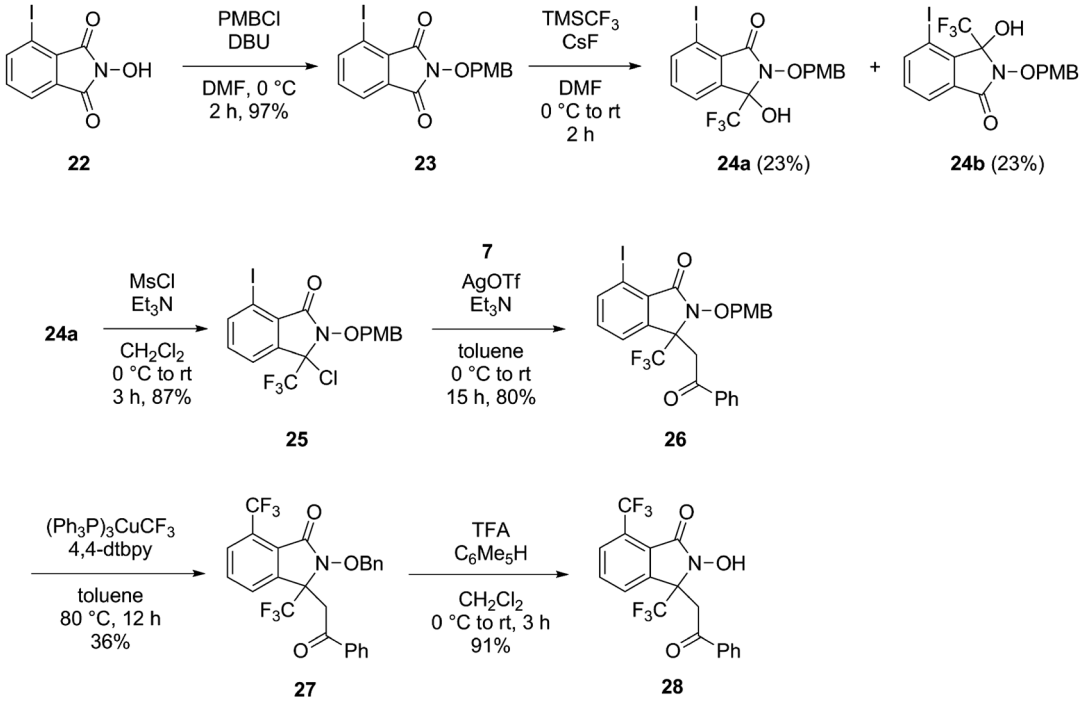


Chart 3. Preparation of 7-Trifluoromethyl *N*-Hydroxy Precatalyst **28**

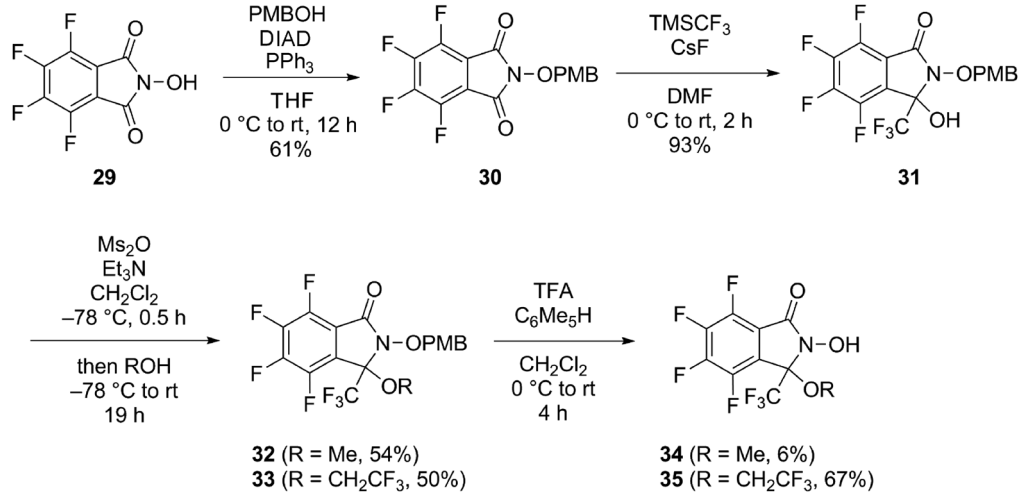
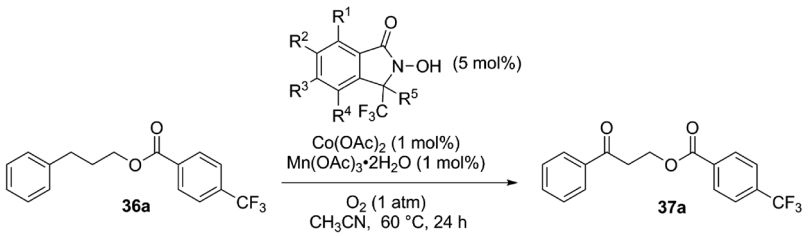


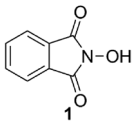
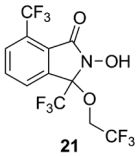
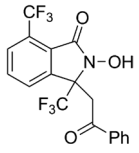
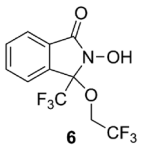
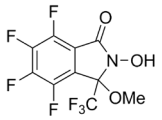
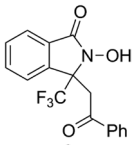
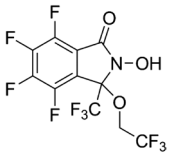
Chart 4. Preparation of 4,5,6,7-Tetrafluoro *N*-Hydroxy Precatalysts **34** and **35**

or acetophenone (**9**) moieties led to improved yields of 45% and 39%, respectively (entries 3, 4). 7-Trifluoromethyl- and 4,5,6,7-tetrafluoro-substituted precatalysts **20** and **34** also afforded improved yields (entries 2 *vs.* 5, 8), probably on account of their increased electron-withdrawing properties. Whereas the combination of the 7-trifluoromethyl and the acetophenone moieties in **28** proved to be mismatched (entries 4 *vs.* 7), the combination of a 7-trifluoromethyl substitution pattern with a 2,2,2-trifluoroethoxy group (**21**) displayed an additive effect, resulting in the formation of ketone **37a** in 66% yield (entries 3, 5 *vs.* 6). The best performance (71% yield, entry 9) was obtained with *N*-hydroxy precatalyst **35**, which contained a 4,5,6,7-tetrafluoro-substituted aromatic ring and a 2,2,2-trifluoroethoxy group.

Subsequently, we examined the scope and limitations of the oxidation of benzylic C–H bonds using precatalyst **35** (Table 2). When 3-phenylpropyl benzoate (**36b**) was used as the substrate, the corresponding ketone **37b** was obtained in 78% yield. *p*-Substituted alkylarenes, bearing either electron-donating or withdrawing substituents such as OMe (**36c**), CF_3 (**36d**), or F (**36e**), all reacted under these conditions to afford ketones **37c–e** in moderate to high yields (42–69%). The high functional group tolerance of the present system is evident from the successful transformation of a variety of alkylbenzenes that bear different functional groups, *e.g.* a carboxylic acid (**36f**), a methyl ester (**36g**), a carboxamide (**36h**), an alkylbromide (**36i**), a nitrile (**36j**), or a methyl imidate (**36k**), into the corresponding ketones **37f–k** in a chemoselective manner (39–80% yield). Interestingly, tetralin (**36l**), xanthene (**36m**), or isochromane (**36n**) were oxidized more readily than alkylarenes, furnishing the corresponding ketones **37l–n** in 41–78% yield even at room temperature.

Table 1. Aerobic Oxidation of Benzylic C–H Bonds in **36a** Using *N*-Oxyl Catalysts



Entry	Catalyst	Yield (%)[a]	Entry	Catalyst	Yield (%)[a]
1[b]	 **1**	92	6	 **21**	66
2	 **5**	23	7	 **28**	28
3	 **6**	45	8	 **34**	46
4	 **9**	39	9	 **35**	71
5	 **20**	46			

a) ^{1}H-NMR yield. *b*) The reaction time was 12 h.

Benzylic Etherification and Acetoamidation Using *N*-Oxyl Radical Catalyst 35 and *N*-Bromosuccinimide (NBS)

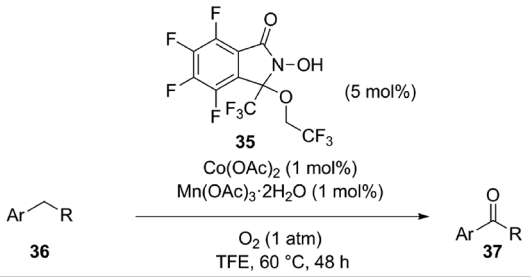
During our investigations on the utility of *N*-hydroxy precatalyst **35**, we discovered novel conditions for the intermolecular benzylic etherification and a Ritter-type reaction that uses NBS as the oxidant (Chart 5). We were thus able to synthesize 2,2,2-trifluoroethylethers, whose preparation *via* the classical Williamson ether procedure is limited by their low nucleophilicity. The conventional synthetic method for the generation of benzylic 2,2,2-trifluoroethylethers involves the nucleophilic attack of TFE to the corresponding benzylic cation, which is generated from a prefunctionalized benzylic compound.[26–28] To the best of our knowledge, the direct transformation of a benzylic sp^3 C–H bond into a C–OCH_2CF_3 moiety has not been reported so far. For that purpose, **36b** was treated with a catalytic amount of **35** to mediate this 2,2,2-trifluoroetherification, which afforded **38** in modest yield (54%).[29]

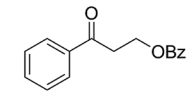
Ritter-type aminations of benzylic sp^3 C–H bonds usually require harsh conditions, *i.e.* heating and/or the presence of a strong oxidant such as *N*-fluoro-*N*′-(chloromethyl)-triethylenediamine pentafluoro phosphate (F-TEDA-PF_6) or ceric ammonium nitrate.[30–33] We found that **36b** could be successfully aminated under mild conditions in CH_3CN to afford 2,2,2-trifluoroethylether **39** in 49% yield using **35**. These reactions may proceed *via* a carbocation intermediate generated by a two-electron oxidation process.[33]

Conclusion

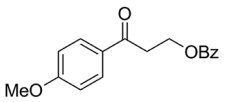
We have developed a synthetic procedure to prepare highly tunable, nonplanar, and electron-deficient *N*-oxyl radical species that can be used for the catalytic aerobic oxidation of benzylic C–H bonds. This method is based on the introduction of a CF_3-substituted sp^3-carbon as an additional functionalization site in close proximity to the *N*-hydroxy moiety of **1**. Subsequently, modulation of the catalyst activity was accomplished by changing the substituents at both the aromatic ring and at the α-position with respect to the CF_3 group. In general, the introduction of more electron-withdrawing groups led to a significant improvement of the catalyst activity, which is in

Table 2. Substrate Scope of the Oxidation of Benzylic C–H Bonds with *N*-Hydroxy Precatalyst **35**[a)]

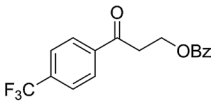




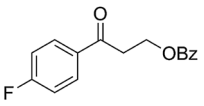
37b (78%)



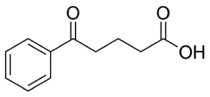
37c (42%)



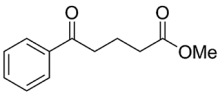
37d (44%)



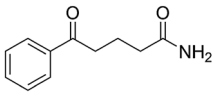
37e (69%)



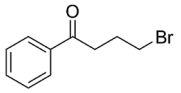
37f (45%)



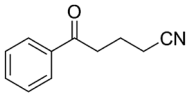
37g (74%)



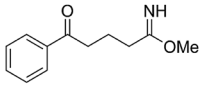
37h (39%)



37i (72%)

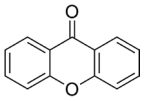


37j (80%)

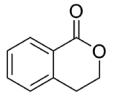


37k (78%)

37l (41%) [r.t.]



37m (64%) [r.t.]



37n (78%) [r.t.]

a) Percentage values in parentheses refer to isolated yields.

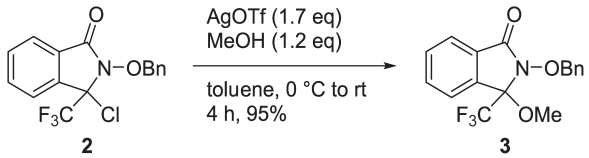
good agreement with previously reported results.[34)] Although the best precatalyst performance still remains inferior to that of **1** itself, these investigations provide fundamental information on the design of novel *N*-oxyl radical catalysts and effective radical directing activators.[16)] Further studies on the functionalization of these compounds that may eventually lead to more active and selective catalysts are ongoing in our laboratory and results will be reported elsewhere in due course.

Experimental

General Method NMR spectra were recorded on JEOL JNM-LA500, JEOL ECX500 (500 MHz for ^{1}H-NMR and 125 MHz for ^{13}C-NMR), and JEOL ECS400 (400 MHz for ^{1}H-NMR, 100 MHz for ^{13}C-NMR, and 368 MHz for ^{19}F-NMR) spectrometer. Chemical shifts were reported downfield from tetramethylsilane (TMS) (δ=0 ppm) for ^{1}H-NMR. For ^{13}C-NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference. For ^{19}F-NMR, chemical shifts were reported downfield from hexafluorobenzene (δ=−164.9 ppm). IR spectra were recorded on a JASCO FT/IR 410 Fourier transform IR spectrophotometer. Electrospray ionization (ESI)-MS spectra were measured on a Waters ZQ4000 spectrometer (for low resolution (LR)-MS), and a JEOL JMS-T100LC AccuTOF spectrometer (for high resolution (HR)-MS). Column chromatographies were performed with silica gel Merck 60 (230–400 mesh ASTM). All reactions other than substrates synthesis were carried out in dry solvents (purchased from Aldrich, Kanto Chemical Co., Inc. or Wako Pure Chemical Industries, Ltd.). Other reagents of which preparation is not described in this manuscript were purchased from Aldrich, Tokyo Chemical Industry Co., Ltd. (TCI), Kanto Chemical Co., Inc., and Wako Pure Chemical Industries, Ltd., and used without further purification. NMR yield was calculated by ^{1}H-NMR of crude product using an internal standard (1,3,5-trioxane).

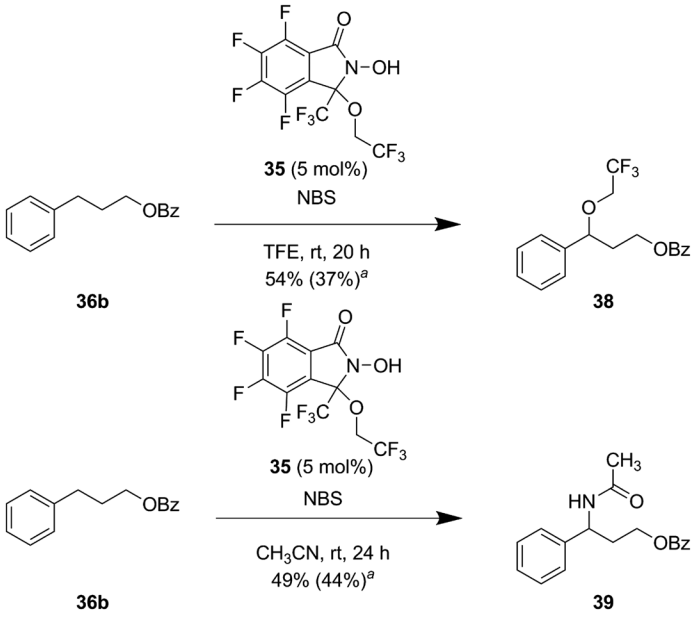
Preparation of *N*-Hydroxy Precatalysts Full spectroscopic data were described for new compounds. Compound **2**,[16)] **22**,[20)] and **29**[22)] were prepared following the reported procedures.

General Procedure for Etherification (Procedure A)



2-Benzyloxy-3-methoxy-3-trifluoromethylisoindolin-1-one (**3**)

To a suspension of silver trifluoromethanesulfonate (AgOTf) (2.18 g, 8.50 mmol) in toluene (5 mL), chloride **2** (1.71 g, 5.00 mmol) in toluene (5 mL) and MeOH (243 μL, 6.00 mmol) were added at 0°C. The reaction mixture was stirred for 1 h at 0°C, and for 3 h at room temperature (rt). Brine was added to the mixture, and the suspension was filtered over Celite. The filtered organic layer was separated, washed with H_2O and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified with flash col-

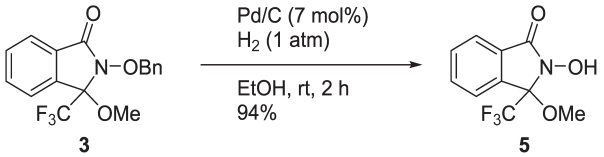


a) Percentage values refer to ^{1}H-NMR yields using 2,4,6-trioxane as an internal standard. Percentage values in parentheses refer to isolated yields.

Chart 5. Benzylic Etherification and Acetoamidation with *N*-Hydroxy Precatalyst **35**

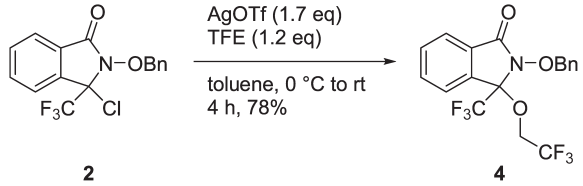
umn chromatography (SiO_2, *n*-hexane–EtOAc=9 : 1→4 : 1) to afford methylether **3** (1.60 g, 95%). White powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.89 (d, J=7.2 Hz, 1H), 7.51–7.72 (m 5H), 7.32–7.42 (m, 3H), 5.30 (d, J=9.9 Hz, 1H), 5.13 (d, J=9.9 Hz, 1H), 2.99 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 165.56, 134.55, 134.47, 133.52, 131.75, 130.10, 129.45 (2C), 128.86, 128.41 (2C), 124.28, 124.19, 122.07 (q, J=285.6 Hz), 91.37 (q, J=32.9 Hz), 79.09, 51.28; ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −77.92 (s, 3F); IR (KBr, cm^{-1}) ν: 3586, 3443, 2939, 1742, 1654, 1559, 1541, 1185, 671; LR-MS (ESI): m/z 360 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{17}H_{14}F_3NO_3Na$ $[M+Na]^+$ 360.0818. Found 360.0831.

General Procedure for Hydrogenolysis of Benzyl Ether (Procedure B)



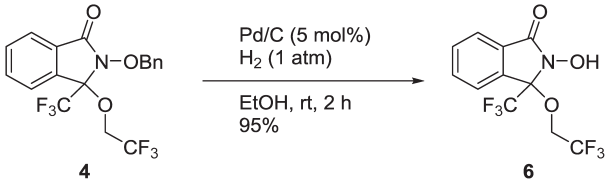
2-Hydroxy-3-methoxy-3-trifluoromethylisoindolin-1-one (**5**)

A suspension of benzylether **3** (1.48 g, 4.39 mmol) and 10 wt% Pd/C (319 mg, 0.300 mmol) in EtOH (12.0 mL) was stirred for 2 h under H_2 atmosphere (1 atm, balloon). The mixture was purged with Ar and filtered over Celite. The filtrate was evaporated under reduced pressure. The residue was purified with flash column chromatography (SiO_2, *n*-hexane–EtOAc=2 : 1→1 : 1) to afford **5** (1.02 g, 94%). White powder; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.82 (d, J=7.6 Hz, 1H), 7.57–7.70 (m, 3H), 3.13 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 165.92, 134.58, 131.69, 130.06, 124.16, 124.05, 121.88 (q, J=286.2 Hz), 91.40 (q, J=33.1 Hz), 51.58; ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −78.41 (s, 3F); IR (KBr, cm^{-1}) ν: 3136, 2952, 2887, 1711, 1471, 1315, 1195, 1124, 1086, 1007, 878, 731; LR-MS (ESI): m/z 270 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{10}H_8F_3NO_3Na$ $[M+Na]^+$ 270.0348. Found 270.0341.



2-Benzyloxy-3-(2,2,2-trifluoroethoxy)-3-trifluoromethylisoindolin-1-one (**4**)

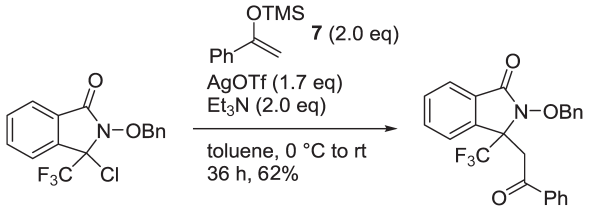
According to the procedure A in which 2,2,2-trifluoroenthanol was used as the alcohol instead, chloride **2** (1.71 g, 5.00 mmol) was converted into ether **4** (1.57 g, 78%). Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.92 (d, J=7.5 Hz, 1H), 7.74 (dd, J=7.4, 7.4 Hz, 1H), 7.69 (dd, J=7.4, 7.4 Hz, 1H), 7.60 (d, J=6.9 Hz, 1H), 7.54 (d, J=7.4 Hz, 2H), 7.35–7.44 (m, 3H), 5.30 (d, J=9.8 Hz, 1H), 5.16 (d, J=9.8 Hz, 1H), 3.40–3.50 (m, 1H), 3.19–3.29 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 165.63, 134.37, 134.23 (2C), 133.53, 132.54 (2C), 129.78, 129.42, 129.07, 128.56, 124.62, 124.58, 122.72 (q, J=277.1 Hz), 121.57 (q, J=286.7 Hz), 91.0 (q, J=33.6 Hz), 79.31, 61.3 (q, J=36.0 Hz); ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −74.02 (s, 3F), −77.52 (s, 3F); IR (neat, cm^{-1}) ν: 3433, 2917, 2848, 1750, 1470, 1293, 1190, 984, 766, 635; LR-MS (ESI): m/z 428 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{18}H_{13}F_6NO_3Na$ $[M+Na]^+$ 428.0692. Found 428.0690.



2-Hydroxy-3-(2,2,2-trifluoroethoxy)-3-trifluoromethylisoindolin-1-one (**6**)

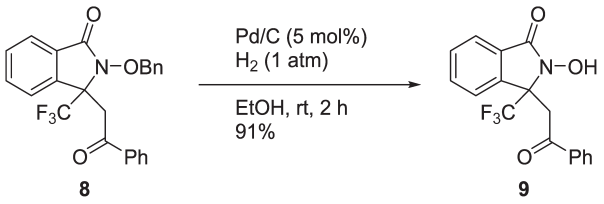
According to the procedure B, benzyl ether **4** (1.45 g, 3.58 mmol) was converted into **6** (1.07 g, 95%). White powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 7.71–7.90 (m, 4H),

3.97–4.10 (m, 1H), 3.64–3.78 (m, 1H); ^{13}C-NMR (125 MHz, acetone-d_6) δ: 164.68, 134.69, 134.11, 133.45, 131.47, 125.54, 124.73, 124.43 (q, J=277.1 Hz), 122.59 (q, J=285.5 Hz), 91.49 (q, J=33.6 Hz), 61.95 (q, J=36.0 Hz); ^{19}F-NMR (368 MHz, acetone-d_6) δ: −74.80 (s, 3F), −78.38 (s, 3F); IR (KBr, cm^{-1}) ν: 3426, 3137, 2942, 1719, 1616, 1508, 1473, 1427, 1378, 1305, 1172, 1125, 1087, 1038, 993, 968, 882, 766; LR-MS (ESI): m/z 338 [M+Na]$^+$; HR-MS (ESI): m/z Calcd for $C_{11}H_7F_6NO_3Na$ [M+Na]$^+$ 338.0222. Found 338.0223.



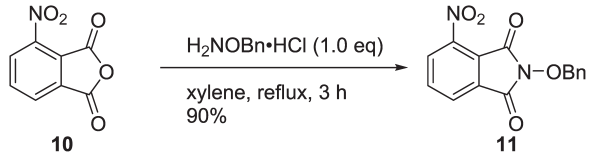
2-Benzyloxy-3-(2-oxo-2-phenylethyl)-3-trifluoromethyl-isoindolin-1-one (**8**)

To a suspension of AgOTf (437 mg, 1.70 mmol) in toluene (1.0 mL), chloride **2** (342 mg, 1.00 mmol), Et_3N (279 μL, 2.00 mmol) and [(1-phenyl-1-ethenyl)oxy]trimethylsilane (**7**) (385 mg, 2.00 mmol) in toluene (1.0 mL) were added at 0°C. The reaction mixture was stirred for 1 h at 0°C, and for 35 h at rt. Brine was added to the mixture and the suspension was filtered over Celite. The organic layer was separated, washed with H_2O and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified with flash column chromatography (SiO_2, n-hexane–EtOAc= 9 : 1→4 : 1) to afford **8** (264 mg, 62%). White powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.90–7.96 (m, 1H), 7.72 (dd, J=7.2, 1.3 Hz, 2H), 7.71–7.59 (m 6H), 7.27–7.37 (m, 5H), 5.43 (d, J=9.9 Hz, 1H), 5.05 (d, J=9.9 Hz, 1H), 4.00 (d, J=17.5 Hz, 1H), 3.74 (d, J=17.5 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 195.56, 168.49, 137.90, 136.05, 134.61, 133.46, 132.91, 130.56, 130.12, 129.43 (2C), 128.65, 128.45 (2C), 128.30 (2C), 127.80, 124.58 (q, J=284.7 Hz), 124.15 (2C), 122.31, 79.20, 67.20 (q, J=29.1 Hz), 34.31; ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −76.46 (s, 3F); IR (KBr, cm^{-1}) ν: 3450, 3061, 3035, 2968, 2926, 1733, 1698, 1594, 1469, 1374, 1275, 1185, 991, 751; LR-MS (ESI): m/z 448 [M+Na]$^+$; HR-MS (ESI): m/z Calcd for $C_{24}H_{18}F_3NO_3Na$ [M+Na]$^+$ 448.1131. Found 448.1140.



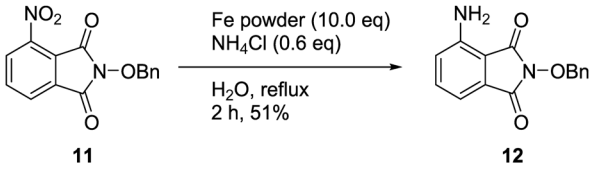
2-Hydroxy-3-(2-oxo-2-phenylethyl)-3-trifluoromethyl-isoindolin-1-one (**9**)

According to the procedure B, benzyl ether **8** (740 mg, 1.74 mmol) was converted into **9** (530 mg, 91%). Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.77 (d, J=7.4 Hz, 2H), 7.70 (d, J=7.5 Hz, 1H), 7.42–7.55 (m, 4H), 7.38 (dd, J=7.5, 7.5 Hz, 2H), 4.02–4.21 (m, 1H), 3.75–3.93 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 193.39, 168.14, 137.61, 136.23, 133.71, 132.66, 130.41, 130.07 (2C), 128.62 (2C), 128.01, 124.14, 124.13 (q, J=285.5 Hz), 122.41, 67.98 (q, J=34.8 Hz), 34.21; ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −76.68 (s, 3F); IR (KBr, cm^{-1}) ν: 3422, 2926, 1696, 1643, 1278, 1185, 754; LR-MS (ESI): m/z 358 [M+Na]$^+$; HR-MS (ESI): m/z Calcd for $C_{17}H_{12}F_3NO_3Na$ [M+Na]$^+$ 358.0661. Found 358.0677.



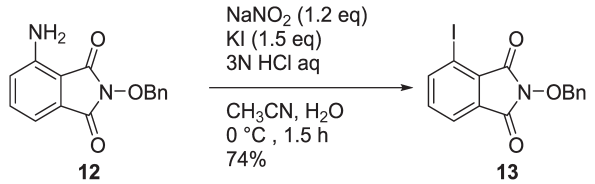
2-Benzyloxy-4-nitroisoindoline-1,3-dione (**11**)

A suspension of 3-nitrophthalic anhydride **10** (1.00 g, 5.18 mmol) and $H_2NOBn\cdot HCl$ (827 mg, 5.18 mmol) in xylene (19 mL) was heated to reflux for 3 h with Dean–Stark apparatus. The mixture was evaporated under reduced pressure. The residue was triturated with EtOH to afford **11** (1.39 g, 90%). Pale yellow powder; ^{1}H-NMR (500 MHz, DMSO-d_6) δ: 8.30 (d, J=8.0 Hz, 1H), 8.15 (d, J=8.0 Hz, 1H), 8.06 (dd, J=8.0, 8.0 Hz, 1H), 7.50–7.55 (m, 2H), 7.38–7.45 (m, 3H), 5.17 (s, 2H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 161.17, 158.81, 144.11, 136.42, 134.02, 130.53, 129.66 (2C), 129.18, 128.69, 128.52 (2C), 127.03, 120.62, 79.48; IR (KBr, cm^{-1}) ν: 3449, 3109, 3048, 2952, 2896, 1793, 1732, 1545, 1350, 1144, 1005, 865, 699; LR-MS (ESI): m/z 321 [M+Na]$^+$; HR-MS (ESI): m/z Calcd for $C_{15}H_{11}N_2O_5Na$ [M+Na]$^+$ 321.0482. Found 321.0497.



4-Amino-2-benzyloxyisoindoline-1,3-dione (**12**)

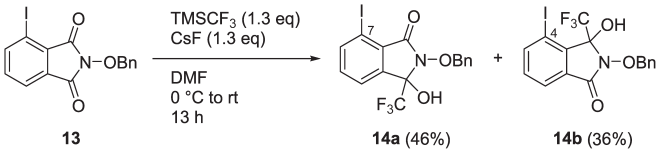
A suspension of **11** (34.0 g, 0.114 mol), Fe powder (63.7 g, 1.14 mol), and NH_4Cl (3.66 g, 0.0684 mol) in H_2O (380 mL) was heated to reflux for 2 h. The mixture was diluted with H_2O and CH_2Cl_2, and filtered over Celite. The organic layer was separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was triturated with Et_2O to afford amine **12** (15.4 g, 51%). Yellow powder; ^{1}H-NMR (400 MHz, DMSO-d_6) δ: 7.32–7.57 (m, 6H), 6.89–7.04 (m, 2H), 6.50 (br s, 2H), 5.11 (s, 2H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 164.58, 163.36, 146.56, 135.43, 134.32, 129.56 (2C), 128.98 (2C), 128.41 (2C), 122.14, 111.05, 105.05, 79.07; IR (KBr, cm^{-1}) ν: 3479, 3336, 3032, 1759, 1715, 1630, 1481, 1385, 1181, 1026, 903, 730; LR-MS (ESI): m/z 291 [M+Na]$^+$; HR-MS (ESI): m/z Calcd for $C_{15}H_{12}N_2O_3Na$ [M+Na]$^+$ 291.0740. Found 291.0732.



2-Benzyloxy-4-iodoisoindoline-1,3-dione (**13**)

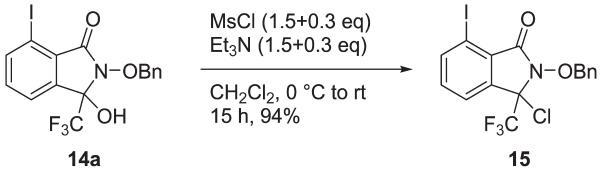
To a suspension of amine **12** (15.4 g, 57.4 mmol) and 3 N HCl aq. (165 mL) in CH_3CN (674 mL), $NaNO_2$ (4.75 g, 68.9 mmol) in H_2O (57.4 mmol) was added dropwise at 0°C, and the mixture was stirred for 0.5 h at the same temperature. To the mixture, KI (14.3 g, 86.1 mmol) in H_2O (57.4 mL) was added at 0°C, and the mixture was stirred for 1 h at the same temperature. To the

mixture, CH_2Cl_2 was added, and the phases were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with 20% $Na_2S_2O_3$ aq., H_2O, and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was triturated with *n*-hexane–EtOAc=2 : 1 to afford iodide **13** (16.1 g, 74%). white powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.09 (d, J=8.1 Hz, 1H), 7.78 (d, J=7.2 Hz, 2H), 7.49–7.54 (m, 2H), 7.32–7.42 (m, 3H), 5.19 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 162.34, 161.39, 145.55, 134.94, 133.44, 130.82, 129.80 (2C), 129.53, 129.33, 128.52 (2C), 123.21, 88.76, 79.94; IR (KBr, cm^{-1}) ν: 3501, 3079, 3033, 1790, 1742, 1455, 1391, 1146, 984, 876, 718; LR-MS (ESI): m/z 402 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{16}H_{11}F_3INO_3Na$ $[M+Na]^+$ 401.9598. Found 401.9590.



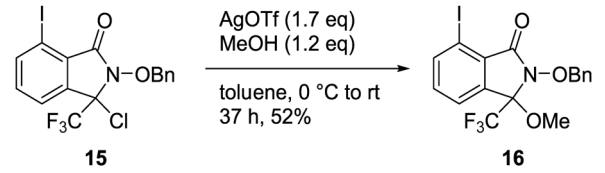
2-Benzyloxy-3-hydroxy-7-iodo-3-trifluoromethylisoindolin-1-one (**14a**) and 4-Iodo Isomer (**14b**)

To a solution of phthalimide **13** (16.0 g, 42.2 mmol) and CsF (8.34 g, 54.9 mmol) in *N*,*N*-dimethylformamide (DMF) (422 mL), trimethyl(trifluoromethyl)silane$_3$ ($TMSCF_3$) (8.13 mL, 54.9 mmol) was added dropwise at 0°C. The mixture was stirred for 0.5 h at 0°C, then for 12 h at rt. To the mixture, H_2O was added at 0°C, and the whole was extracted with EtOAc for 3 times. The combined organic layer was washed with 1 N HCl aq., H_2O for 3 times, and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was triturated with Et_2O to afford alcohol **14a** (6.54 g, 35%). The mother liquor was evaporated under reduced pressure, and the residue was purified with flash column chromatography (SiO_2, *n*-hexane–EtOAc=9 : 1→1 : 1) to afford alcohol **14a** (2.11 g, 11%) and **14b** (6.86 g, 36%). Compound **14a**: White powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 8.16 (dd, J=7.6, 0.9 Hz, 1H), 7.81 (dd, J=7.6, 0.9 Hz, 1H), 7.51–7.60 (m, 3H), 7.35–7.46 (m, 3H), 5.31 (d, J=9.4 Hz, 2H), 5.19 (d, J=9.4 Hz, 2H); ^{13}C-NMR (100 MHz, acetone-d_6) δ: 163.88, 143.81, 141.61, 135.89, 135.52, 130.22 (2C), 129.57 (2C), 129.19 (2C), 124.96 (q, J=1.9 Hz), 123.57 (q, J=286.6 Hz), 89.65, 86.33 (q, J=33.8 Hz), 80.52; ^{19}F-NMR (368 MHz, acetone-d_6) δ: −79.43 (s, 3F); IR (KBr, cm^{-1}) ν: 3254, 3031, 1717, 1460, 1376, 1198, 989, 946, 794, 714; LR-MS (ESI): m/z 472 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{16}H_{11}F_3INO_3Na$ $[M+Na]^+$ 471.9628. Found 471.9618. Compound **14b**: white powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 8.25 (d, J=7.6 Hz, 1H), 7.85 (d, J=7.6 Hz, 1H), 7.56 (d, J=7.2 Hz, 2H), 7.34–7.49 (m 4H), 5.29 (d, J=9.9 Hz, 1H), 5.22 (d, J=9.9 Hz); ^{13}C-NMR (100 MHz, acetone-d_6) δ: 162.90, 146.79, 139.73, 136.00, 133.77, 132.91, 130.10 (2C), 129.49, 129.12 (2C), 124.14, 123.93 (q, J=290.3 Hz), 90.14 (q, J=32.9 Hz), 90.10, 80.84; ^{19}F-NMR (368 MHz, acetone-d_6) δ: −75.41 (s, 3F); IR (KBr, cm^{-1}) ν: 3169, 2956, 2885, 1702, 1574, 1461, 1372, 1251, 1191, 1092, 870, 760, 700; LR-MS (ESI): m/z 472 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{16}H_{11}F_3INO_3Na$ $[M+Na]^+$ 471.9628. Found 471.9624.



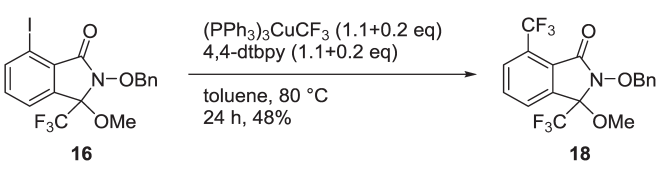
2-Benzyloxy-3-chloro-7-iodo-3-trifluoromethylisoindolin-1-one (**15**)

To a suspension of alcohol **14a** (8.64 g, 19.2 mmol) in CH_2Cl_2 (192 mL), Et_3N (4.26 mL, 28.8 mmol) and MsCl (2.23 mL, 30.7 mmol) were added at 0°C, and the mixture was stirred for 0.5 h at 0°C, then for 13 h at rt. To the mixture, Et_3N (798 μL, 5.76 mmol) and MsCl (446 μL, 5.76 mmol) were added at rt, and the mixture was stirred for 1 h at rt. To the mixture, H_2O was added and the phases were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified with flash column chromatography (SiO_2, *n*-hexane–EtOAc=19 : 1→9 : 1) to afford chloride **15** (8.46 g, 94%). white powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 8.28 (dd, J=9.3, 0.9 Hz, 1H), 7.93 (dd, J=7.7, 0.9 Hz, 1H), 7.67 (dd, J=7.6, 7.6 Hz, 1H), 7.57–7.62 (m, 2H), 7.41–7.49 (m, 3H), 5.42 (d, J=9.4 Hz, 1H), 5.27 (d, J=9.4 Hz, 1H); ^{13}C-NMR (100 MHz, acetone-d_6) δ: 163.85, 144.63, 140.68, 136.46, 135.07, 130.46 (2C), 129.93, 129.33 (2C), 128.34, 125.13 (q, J=1.9 Hz), 122.46 (q, J=283.8 Hz), 90.85, 80.48, 79.00 (q, J=36.6 Hz); ^{19}F-NMR (368 MHz, acetone-d_6) δ: −76.34 (s, 3F); IR (KBr, cm^{-1}) ν: 3484, 3069, 3033, 2960, 2897, 1752, 1456, 1264, 1171, 977, 903, 713; LR-MS (ESI): m/z 490 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{16}H_{10}ClF_3INO_2Na$ $[M+Na]^+$ 489.9289. Found 489.9300.



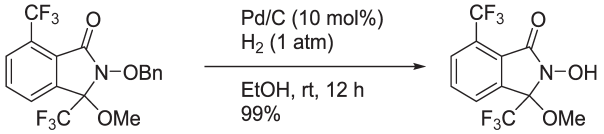
2-Benzyloxy-7-iodo-3-methoxy-3-(trifluoromethyl)-isoindolin-1-one (**16**)

According to the procedure A, the chloride **15** (4.09 g, 8.75 mmol) was converted into ether **16** (2.09 g, 52%). white powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 8.23 (d, J=8.1 Hz, 1H), 7.76 (d, J=7.6 Hz, 1H), 7.56–7.63 (m, 3H), 7.35–7.46 (m, 3H), 5.29 (d, J=10.0 Hz, 1H), 5.20 (d, J=10.0 Hz, 1H), 3.13 (s, 3H); ^{13}C-NMR (100 MHz, acetone-d_6) δ: 164.68, 144.40, 137.53, 135.84, 135.68, 131.27, 130.16 (2C), 129.65, 129.24 (2C), 125.44, 122.93 (q, J=285.6 Hz), 90.82 (q, J=32.9 Hz), 90.32, 79.88, 51.83; ^{19}F-NMR (368 MHz, acetone-d_6) δ: −78.29 (s, 3F); IR (KBr, cm^{-1}) ν: 3466, 3077, 3029, 2965, 2898, 1742, 1456, 1276, 1187, 986, 869, 724, 697; LR-MS (ESI): m/z 486 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{17}H_{13}F_3INO_3Na$ $[M+Na]^+$ 485.9784. Found 485.9781.



2-Benzyloxy-3-methoxy-3,7-bistrifluoromethylisoindolin-1-one (**18**)

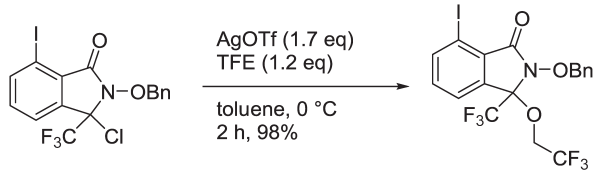
The mixture of iodide **16** (100 mg, 0.216 mmol), $(PPh_3)_3CuCF_3$ (218 mg, 0.237 mmol) and 4,4′-di-*tert*-butyl-2,2′-bipyridyl (4,4′-dtbpy) (63.6 mg, 0.237 mmol) in toluene (2.2 mL) was stirred for 20 h at 80°C. To the mixture, $(PPh_3)_3CuCF_3$ (39.7 mg, 0.0432 mmol) and 4,4′-di-*tert*-butyl-2,2′-bipyridyl (11.6 mg, 0.0432 mmol) were added and the mixture was stirred for 4 h at 80°C. The mixture was diluted with EtOAc, washed with H_2O, 28% NH_3 aq., H_2O and brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified with flash column chromatography (SiO_2, *n*-hexane–EtOAc=19 : 1→9 : 1) to afford trifluoromehylated compound **18** (41.7 mg, 48%). White powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.94 (dd, J=4.3 Hz, 1H), 7.81 (d, J=4.3 Hz, 2H), 7.54 (d, J=5.9 Hz, 2H), 7.32–7.44 (m, 3H), 5.32 (d, J=9.7 Hz, 1H), 5.13 (d, J=9.7 Hz, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 162.44, 137.00, 134.30, 133.52, 129.63 (2C), 129.23 (q, J=4.8 Hz), 129.04 (2C), 128.53, 127.74, 127.83, (q, J=28.8 Hz), 127.81, 122.00 (q, J=274.8 Hz), 121.86 (q, J=286.7 Hz), 97.78 (q, J=36.0 Hz), 79.20, 51.49; ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −60.96 (s, 3F), −77.67 (s, 3F); IR (KBr, cm^{-1}) ν: 3584, 3388, 2918, 2847, 1755, 1604, 1325, 1173, 989, 760, 641; LR-MS (ESI): m/z 428 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{18}H_{13}F_6NO_3Na$ $[M+Na]^+$ 428.0692. Found 428.0701.



18 **20**

2-Hydroxy-3-methoxy-3,7-bistrifluoromethylisoindolin-1-one (**20**)

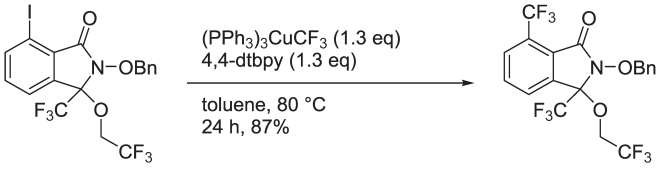
According to the procedure B, the benzyl ether **18** (38.0 mg, 0.0938 mmol) was converted into **20** (29.4 mg, 99%). White powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.76–7.92 (m, 3H), 3.17 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 162.91, 137.07, 133.36, 129.11, 127.78 (q, J=36.0 Hz), 127.61, 127.56, 121.89 (q, J=273.5 Hz), 121.55 (q, J=286.7 Hz), 90.60 (q, J=33.6 Hz), 51.65; ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −60.86 (s, 3F), −78.04 (s, 3F); IR (KBr, cm^{-1}) ν: 3426, 3178, 2954, 1734, 1610, 1509, 1329, 1195, 1135, 1016, 983, 878, 812, 704; LR-MS (ESI): m/z 338 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{11}H_7F_6NO_3Na$ $[M+Na]^+$ 338.0222. Found 338.0226.



15 **17**

2-Benzyloxy-7-iodo-3-(2,2,2-trifluoroethoxy)-3-trifluoromethylisoindolin-1-one (**17**)

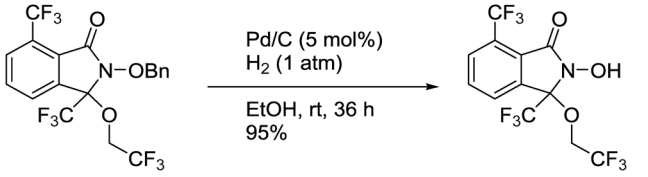
According to the procedure A in which 2,2,2-trifluoroenthanol was used as the alcohol instead, the chloride **15** (0.935 g, 2.00 mmol) was converted into ether **17** (1.04 g, 98%). White powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 8.27 (dd, J=7.6, 0.9 Hz, 1H), 7.84 (d, J=8.1 Hz, 1H), 7.64 (dd, J=7.6, 7.6 Hz, 1H), 7.63 (dd, J=7.6, 1.8 Hz, 2H), 7.37–7.48 (m, 3H), 5.26–5.33 (m, 2H), 4.00–4.11 (m, 1H), 3.82–3.94 (m, 1H); ^{13}C-NMR (100 MHz, acetone-d_6) δ: 164.82, 145.00, 136.40, 136.08, 135.67, 131.28, 130.14, 129.77, 129.34, 125.76 (q, J=1.9 Hz), 124.36 (q, J=276.3 Hz), 122.50 (q, J=286.6 Hz), 90.86, 90.59 (q, J=32.9 Hz), 80.23, 62.20 (q, J=35.7 Hz); ^{19}F-NMR (368 MHz, acetone-d_6) δ: −74.61 (s, 3F), −77.85 (s, 3F); IR (KBr, cm^{-1}) ν: 3482, 3034, 2941, 2873, 1754, 1584, 1463, 1283, 1190, 1002, 953, 874, 798, 727; LR-MS (ESI): m/z 554 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{18}H_{12}F_6INO_3Na$ $[M+Na]^+$ 553.9658. Found 553.9634.



17 **19**

2-Benzyloxy-3-(2,2,2-trifluoroethoxy)-3,7-bistrifluoromethylisoindolin-1-one (**19**)

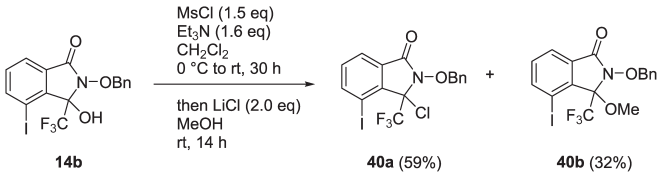
According to the procedure described for the preparation of the trifluoromehyl compound **18** from iodide **16**, the iodide **17** (444 mg, 0.837 mmol) was converted into trifluoromethyl compound **19** (346 mg, 87%). White powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.98 (d, J=4.5 Hz, 1H), 7.86 (d, J=4.5 Hz, 1H), 7.52 (d, J=5.4 Hz, 2H), 7.37–7.41 (m, 3H), 5.32 (d, J=9.9 Hz, 1H), 5.16 (d, J=9.9 Hz, 1H), 3.40–3.52 (m, 1H), 3.13–3.24 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 162.45, 136.03, 134.25, 134.15, 129.98 (q, J=6.0 Hz), 129.56 (2C), 129.23 (2C), 128.65 (2C), 128.3 (q, J=34.8 Hz), 128.04, 122.59 (q, J=277.1 Hz), 121.85 (q, J=274.7 Hz), 121.38 (q, J=286.7 Hz), 90.18 (q, J=34.8 Hz), 79.40, 61.51 (q, J=36.0 Hz); ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −61.05 (s, 3F), −74.06 (s, 3F), −77.24 (s, 3F); IR (KBr, cm^{-1}) ν: 3512, 3439, 3043, 2967, 2898, 1770, 1611, 1330, 1182, 980, 873, 820, 693; LR-MS (ESI): m/z 496 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{19}H_{12}F_9NO_3Na$ $[M+Na]^+$ 496.0566. Found 496.0546.



19 **21**

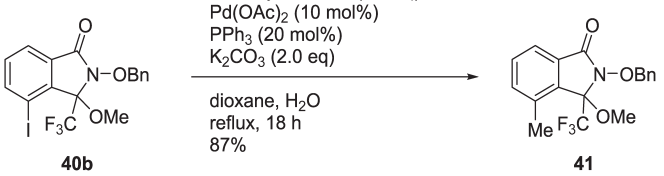
2-Hydroxy-3-(2,2,2-trifluoroethoxy)-3,7-bistrifluoromethylisoindolin-1-one (**21**)

According to the procedure B, the benzyl ether **19** (300 mg, 0.634 mmol) was converted into **21** (233 mg, 95%). White powder; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.94 (d, J=8.0 Hz, 1H), 7.83–7.91 (m, 2H), 4.01–4.12 (m, 1H), 3.31–3.38 (m, 1H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 163.18, 136.15, 134.12, 129.82 (q, J=6.0 Hz), 128.07 (q, J=36.0 Hz), 127.96, 127.15, 122.71 (q, J=277.1 Hz), 121.73 (q, J=273.5 Hz), 121.10 (q, J=286.7 Hz), 90.13 (q, J=33.6 Hz), 61.86 (q, J=37.2 Hz); ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −61.14 (s, 3F), −74.33 (s, 3F), −77.55 (s, 3F); IR (KBr, cm^{-1}) ν: 3419, 3207, 2968, 1724, 1332, 1296, 1178, 984, 885, 811, 689; LR-MS (ESI): m/z 406 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{12}H_6F_9NO_3Na$ $[M+Na]^+$ 406.0096. Found 406.0103.



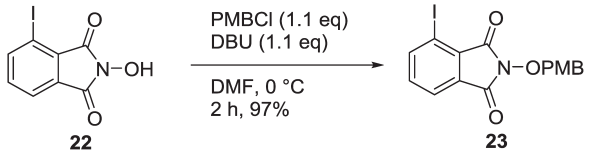
2-Benzyloxy-3-chloro-4-iodo-3-trifluoromethylisoindolin-1-one (**40a**) and 2-Benzyloxy-4-iodo-3-methoxy-3-trifluoromethylisoindolin-1-one (**40b**)

To a solution of alcohol **14b** (1.00 g, 2.23 mmol) in CH_2Cl_2 (22 mL), MsCl (259 μL, 3.35 mmol) and Et_3N (495 μL, 3.57 mmol) were added dropwise at 0°C, and the mixture was stirred for 1 h at 0°C, then for 24 h at rt. To the mixture, MsCl (173 μL, 2.23 mmol) and Et_3N (340 μL, 2.45 mmol) were added at rt and stirred for 3 h at the same temperature. To the mixture, LiCl (189 mg, 4.46 mmol) was added, and stirred for 12 h at rt. To the mixture, MeOH (5.0 mL) was added, stirred for 12 h at rt, then H_2O was added. The phases were separated. The aqueous layer was extracted with CH_2Cl_2. The combined organic layer was washed with H_2O, and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified with flash column chromatography (SiO_2, *n*-hexane–EtOAc=19 : 1→9 : 1) to afford chloride **40a** (630 mg, 59%) and ether **40b** (335 mg, 32%). Chloride **40a**: White powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 8.44 (dd, J=8.1, 1.4 Hz, 1H), 7.99 (dd, J=8.1, 0.9 Hz, 1H), 7.53–7.63 (m, 3H), 7.40–7.48 (m, 3H), 5.42 (d, *J*=9.4 Hz, 1H), 5.35 (d, *J*=9.4 Hz, 1H); ^{13}C-NMR (100 MHz, acetone-d_6) δ: 162.90, 146.79, 139.73, 136.00, 133.77, 132.92, 130.10 (2C), 129.49, 129.12 (2C), 124.14, 123.93 (q, *J*=290.1 Hz), 90.14 (q, *J*=32.9 Hz), 90.10, 80.84; ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −72.02 (s, 3F); IR (KBr, cm^{-1}) *v*: 3462, 3065, 2930, 2878, 1752, 1454, 1173, 1000, 915, 720; LR-MS (ESI): *m/z* 490 $[M+Na]^+$; HR-MS (ESI): *m/z* Calcd for $C_{16}H_{10}ClF_3INO_2Na$ $[M+Na]^+$ 489.9289. Found 489.9283. Ether **40b**: Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 8.12 (dd, *J*=7.6, 0.9 Hz, 1H), 7.88 (dd, *J*=7.6, 0.9 Hz, 1H), 7.53 (dd, *J*=7.2, 1.3 Hz, 2H), 7.32–7.42 (m, 2H), 7.30 (dd, *J*=7.6, 7.6 Hz, 1H), 5.25 (d, *J*=10.3 Hz, 1H), 5.19 (d, *J*=10.3 Hz, 1H), 3.15 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 164.17, 145.94, 136.28, 134.73, 133.15, 132.84, 129.19 (2C), 128.87, 128.46 (2C), 124.12, 122.12 (q, *J*=289.4 Hz), 93.80 (q, *J*=32.9 Hz), 89.95, 78.97, 51.54; ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −73.41 (s, 3F); IR (neat, cm^{-1}) *v*: 3433, 1748, 1640, 1457, 1186, 1122, 1000, 733; LR-MS (ESI): *m/z* 486 $[M+Na]^+$; HR-MS (ESI): *m/z* Calcd for $C_{17}H_{13}F_3INO_3Na$ $[M+Na]^+$ 485.9784. Found 485.9791.



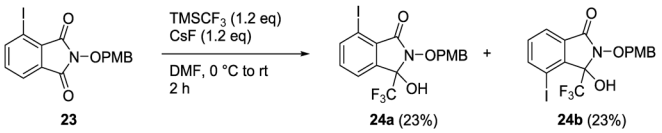
2-Benzyloxy-3-methoxy-4-methyl-3-trifluoromethylisoindolin-1-one (**41**)

The mixture of iodide **40b** (330 mg, 0.712 mmol), trimethylboroxine (0.299 mL, 2.14 mmol), $Pd(OAc)_2$ (16.0 mg, 0.0712 mmol), PPh_3 (37.3 mg, 0.142 mmol), and K_2CO_3 (197 mg, 1.42 mmol) in dioxane (7.1 mL) and H_2O (0.71 mL) was heated to reflux for 18 h. The mixture was diluted with H_2O and extracted with EtOAc twice. The combined organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered and evaporated under reduced pressure. The residue was purified with flash column chromatography (SiO_2, *n*-hexane–EtOAc=19 : 1→9 : 1) to afford compound **41** (217 mg, 87%). Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.72 (d, *J*=7.2 Hz, 1H), 7.30–7.56 (m, 7H), 5.26 (d, *J*=10.3 Hz, 1H), 5.18 (d, *J*=10.3 Hz, 1H), 3.05 (s, 3H), 2.46 (s, 3H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 165.83, 136.41, 136.30, 134.95, 131.56, 131.52, 130.86, 129.26, 128.79, 128.44, 122.55 (q, *J*=287.9 Hz), 121.97, 93.59 (q, *J*=32.4 Hz), 78.92, 51.05, 17.80 (q, *J*=3.6 Hz); ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −75.41 (s, 3F); IR (neat, cm^{-1}) *v*: 3426, 2916, 1746, 1637, 1282, 1193, 1114, 1020, 735; LR-MS (ESI): *m/z* 374 $[M+Na]^+$; HR-MS (ESI): *m/z* Calcd for $C_{18}H_{16}F_3NO_3Na$ $[M+Na]^+$ 374.0974. Found 374.0978.



4-Iodo-2-(4-methoxybenzyloxy)isoindoline-1,3-dione (**23**)

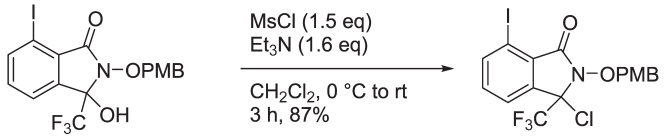
To a solution of 4-iodo-NHPI (**22**) (5.03 g, 17.4 mmol) in DMF (35 mL), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2.60 mL, 19.1 mmol) and PMBCl (2.80 mL, 19.1 mmol) were added at 0°C and the mixture was stirred for 2 h at the same temperature. H_2O was added to the mixture and the resulted suspension was filtered. The collected precipitate was triturated with *i*Pr_2O to afford ether **23** (6.88 g, 97%). Brown powder; ^{1}H-NMR (500 MHz, acetone-d_6) δ: 8.24 (d, *J*=7.5 Hz, 1H), 7.85 (d, *J*=7.5 Hz, 1H), 7.58 (dd, *J*=7.5, 7.5 Hz, 1H), 7.49 (d, *J*=8.6 Hz, 2H), 6.95 (d, *J*=8.6 Hz, 2H), 5.15 (s, 2H), 3.80 (s, 3H); ^{13}C-NMR (125 MHz, acetone-d_6) δ: 163.02, 162.14, 161.40, 146.40, 136.18, 132.37 (2C), 132.15, 130.83, 127.23, 123.76, 114.62 (2C), 88.94, 80.05, 55.54; IR (KBr, cm^{-1}) *v*: 3444, 3078, 2961, 2933, 2837, 1789, 1739, 1611, 1515, 1390, 1252, 1144, 982, 876, 814, 717; LR-MS (ESI): *m/z* 432 $[M+Na]^+$; HR-MS (ESI): *m/z* Calcd for $C_{16}H_{12}INO_4Na$ $[N+Na]^+$ 431.9703. Found 431.9722.



3-Hydroxy-7-iodo-2-(4-methoxybenzyloxy)-3-trifluoromethylisoindolin-1-one (**24a**) and 4-Iodo Isomer (**24b**)

According to the procedure described for the preparation of the alcohol **14a** and **b** from phthalimide **13**, the phthalimide **23** (6.60 g, 16.1 mmol) was converted into alcohol **24a** (1.77 g, 23%) and **24b** (1.74 g, 23%). Alcohol **24a**: White powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 8.15 (dd, *J*=8.1, 0.9 Hz, 1H), 7.80 (d, *J*=8.1 Hz, 1H), 7.54 (dd, *J*=8.1, 8.1 Hz, 1H), 7.50 (d, *J*=8.5 Hz, 2H), 6.97 (d, *J*=8.5 Hz, 2H), 5.24 (d, *J*=9.0 Hz, 1H), 5.12 (d, *J*=9.0 Hz, 1H), 3.81 (s, 3H); ^{13}C-NMR (100 MHz, acetone-d_6) δ: 163.87, 161.15, 143.81, 141.61, 135.49, 132.03 (2C), 130.30, 127.88, 124.94, 123.57 (q, *J*=286.6 Hz), 114.53 (2C), 89.64, 86.25 (q, *J*=32.9 Hz), 80.22, 55.53; ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −79.34 (s, 3F); IR (KBr, cm^{-1}) *v*: 3420, 3186, 2956, 2836, 1717, 1697, 1613, 1517, 1254, 1194, 1092, 976, 827, 708; LR-MS (ESI): *m/z* 502 $[M+Na]^+$; HR-MS (ESI): *m/z* Calcd for $C_{17}H_{13}F_3INO_4Na$ $[M+Na]^+$ 501.9734. Found 501.9740. Alcohol **24b**: White powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 8.24 (dd, *J*=8.1, 0.9 Hz, 1H), 7.84 (dd, *J*=7.6, 1.4 Hz, 1H), 7.41–7.88 (m 3H), 6.95 (d, *J*=9.0 Hz, 2H), 5.21 (d, *J*=9.9 Hz,

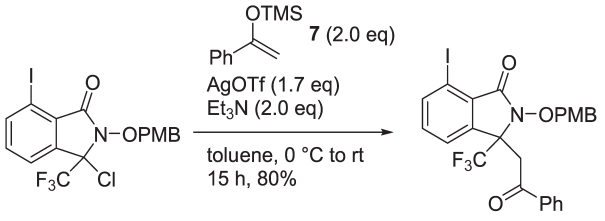
1H), 5.13 (d, J=9.9 Hz, 1H), 3.81 (s, 3H); ^{13}C-NMR (100 MHz, acetone-d_6) δ: 162.87, 161.05, 146.72, 139.74, 133.74, 133.00, 131.93 (2C), 127.96, 124.11, 123.92 (q, J=290.4 Hz), 114.46 (2C), 90.09, 90.07 (q, J=32.9 Hz), 80.56, 55.48; ^{19}F-NMR (368 MHz, acetone-d_6) δ: −75.38 (s, 3F); IR (KBr, cm^{-1}) ν: 3181, 2960, 2836, 1702, 1612, 1516, 1254, 1196, 1131, 983, 833, 756; LR-MS (ESI): m/z 502 [M+Na]$^+$; HR-MS (ESI): m/z Calcd for $C_{17}H_{13}F_3INO_4Na$ [M+Na]$^+$ 501.9734. Found 501.9732.



24a **25**

3-Chloro-7-iodo-2-(4-methoxybenzyloxy)-3-trifluoromethylisoindolin-1-one (**25**)

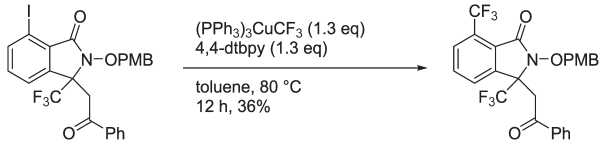
According to the procedure described for the preparation of the chloride **15** from alcohol **14a**, the alcohol **24a** (1.72 g, 3.59 mmol) was converted into chloride **25** (1.55 g, 87%). White powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 8.27 (dd, J=8.1, 0.9 Hz, 1H), 7.92 (d, J=7.6 Hz), 7.66 (dd, J=7.6, 7.6 Hz, 1H), 7.43 (d, J=8.5 Hz, 2H), 6.99 (d, J=8.5 Hz, 2H), 5.34 (d, J=9.0 Hz, 1H), 5.19 (d, J=9.0 Hz, 1H), 3.83 (s, 3H); ^{13}C-NMR (100 MHz, acetone-d_6) δ: 163.78, 161.36, 144.58, 140.68, 136.38, 132.28, 128.40, 127.03, 125.11 (q, J=1.9 Hz), 122.45 (q, J=283.8 Hz), 114.65, 90.79, 80.18, 78.85 (q, J=35.7 Hz), 55.54; ^{19}F-NMR (368 MHz, acetone-d_6) δ: −76.31 (s, 3F); IR (KBr, cm^{-1}) ν: 3422, 2959, 2834, 1742, 1515, 1459, 1249, 974, 706; LR-MS (ESI): m/z 520 [M+Na]$^+$; HR-MS (ESI): m/z Calcd for $C_{17}H_{12}ClF_3INO_3Na$ [M+Na]$^+$ 520.9395. Found 519.9382.



25 **26**

7-Iodo-2-(4-methoxybenzyloxy)-3-(2-oxo-2-phenylethyl)-3-trifluoromethylisoindolin-1-one (**26**)

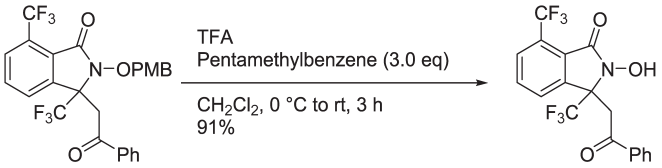
According to the procedure described for the preparation of the phenylketone **8** from chloride **2**, the chloride **25** (498 mg, 1.00 mmol) was converted into acetophenone **26** (464 mg, 80%). White powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 8.09 (d, J=7.6 Hz, 1H), 7.86 (d, J=8.5 Hz, 2H), 7.76 (d, J=7.6 Hz, 1H), 7.56 (dd, J=7.6, 7.6 Hz, 1H), 7.34–7.46 (m, 5H), 6.86 (d, J=8.5 Hz, 2H), 5.27 (d, J=9.4 Hz, 1H), 5.03 (d, J=9.4 Hz, 1H), 4.24 (s, 1H), 4.23 (s, 1H), 3.73 (s, 3H); ^{13}C-NMR (100 MHz, acetone-d_6) δ: 193.71, 167.72, 161.04, 142.37, 142.15, 137.05, 134.86, 134.33, 134.95, 131.95 (2C), 129.39 (2C), 128.73 (2C), 127.99 (q, J=217.1 Hz), 127.80, 123.77, 114.51 (2C), 90.18, 79.49, 66.83 (q, J=29.1 Hz), 55.44, 35.03; ^{19}F-NMR (368 MHz, acetone-d_6) δ: −76.93 (s, 3F); IR (KBr, cm^{-1}) ν: 3436, 3066, 2998, 2955, 2836, 1730, 1695, 1611, 1517, 1259, 1195, 1156, 1002, 822, 688; LR-MS (ESI): m/z 604 [M+Na]$^+$; HR-MS (ESI): m/z Calcd for $C_{25}H_{19}F_3INO_4Na$ [M+Na]$^+$ 604.0203. Found 604.0228.



26 **27**

2-(4-Methoxybenzyloxy)-3-(2-oxo-2-phenylethyl)-3,7-bistrifluoromethylisoindolin-1-one (**27**)

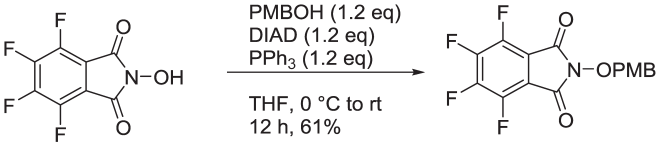
According to the procedure described for the preparation of the trifluoromethylated compound **18** from iodide **16**, the iodide **26** (440 mg, 0.757 mmol) was converted into trifluoromethylated compound **27** (141 mg, 36%). White powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 8.05 (d, J=7.2 Hz, 1H), 8.01 (d, J=7.6 Hz, 1H), 7.86–7.95 (m, 3H), 7.57 (dd, J=7.4, 7.4 Hz, 1H), 7.38–7.61 (m, 4H), 6.86 (d, J=8.5 Hz, 2H), 5.27 (d, J=9.4 Hz, 1H), 5.04 (d, J=9.4 Hz, 1H), 3.74 (s, 3H); ^{13}C-NMR (100 MHz, acetone-d_6) δ: 193.78, 165.85, 161.08, 141.87, 136.95, 134.40, 134.20, 131.98 (2C), 129.40 (2C), 129.25, 128.74 (2C), 128.32 (q, J=5.6 Hz), 127.88, 127.66, 127.27, 125.51 (q, J=284.7 Hz), 123.11 (q, J=272.5 Hz), 114.53 (2C), 79.52, 67.85 (q, J=29.1 Hz), 55.43, 34.97; ^{19}F-NMR (368 MHz, acetone-d_6) δ: −60.90 (s, 3F), −76.96 (s, 3F); IR (KBr, cm^{-1}) ν: 3442, 2957, 1742, 1693, 1612, 1518, 1323, 1255, 1193, 1140, 1006, 812, 867; LR-MS (ESI): m/z 546 [M+Na]$^+$; HR-MS (ESI): m/z Calcd for $C_{26}H_{19}F_6NO_4Na$ [M+Na]$^+$ 546.1110. Found 546.1097.



27 **28**

2-Hydroxy-3-(2-oxo-2-phenylethyl)-3,7-bistrifluoromethylisoindolin-1-one (**28**)

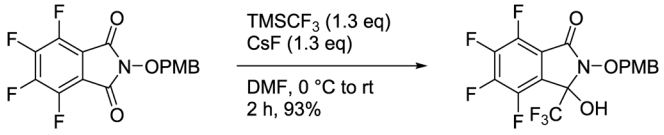
To a solution of PMBether **27** (52.3 mg, 0.100 mmol) and pentamethyl benzene (44.4 mg, 0.300 mmol) in CH_2Cl_2 (2.0 mL), TFA (1.0 mL) was added at 0°C, and the mixture was stirred for 0.5 h at 0°C, then for 2 h at rt. The mixture was neutralized with sat. $NaHCO_3$ aq. at 0°C, then the phases were separated. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified with flash column chromatography (SiO_2, n-hexane–EtOAc=4 : 1→2 : 1) to afford **28** (36.8 mg, 91%). Pale yellow powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 7.81–8.09 (m, 5H), 7.39–7.66 (m, 3H), 4.20–4.39 (m, 2H); ^{13}C-NMR (100 MHz, acetone-d_6) δ: 193.90, 164.41, 141.69, 137.19, 134.40, 133.50, 129.94, 129.48 (2C), 128.79 (2C), 128.06 (q, J=5.6 Hz), 127.73, 127.43, 125.44 (q, J=284.7 Hz), 123.74 (q, J=273.4 Hz), 67.93 (q, J=28.2 Hz), 34.68; ^{19}F-NMR (368 MHz, acetone-d_6) δ: −60.74 (3F), −77.48 (3F); IR (KBr, cm^{-1}) ν: 3422, 3187, 2926, 1720, 1691, 1598, 1327, 1279, 1172, 814, 688; LR-MS (ESI): m/z 426 [M+Na]$^+$; HR-MS (ESI): m/z Calcd for $C_{18}H_{11}F_6NO_3Na$ [M+Na]$^+$ 426.0535. Found 426.0531.



29 **30**

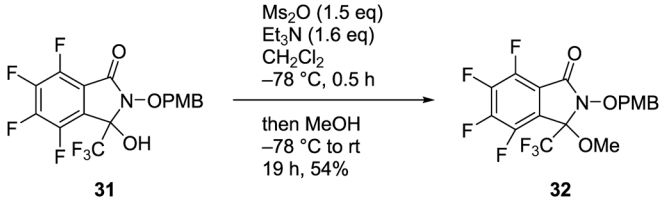
4,5,6,7-Tetrafluoro-2-(4-methoxybenzyloxy)isoindoline-1,3-dione (**30**)

To a solution of phthalimide **29** (1.51 g, 6.42 mmol), 4-methoxylbenzylalcohol (1.06 g, 7.70 mmol) and PPh_3 (2.02 g, 7.70 mmol) in tetrahydrofuran (THF) (13 mL), diisopropyl azodicarboxylate in toluene (4.05 mL, 7.70 mmol) was added at 0°C, and the reaction mixture was stirred for 1 h at 0°C and for 12 h at rt. The reaction mixture was evaporated under reduced pressure. The residue was triturated with EtOAc to afford benzylether **30** (1.40 g, 61%). Pale yellow powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 7.47 (d, J=8.5 Hz, 2H), 6.95 (d, J=8.5 Hz, 2H), 5.13 (s, 2H), 3.81 (s, 3H); ^{13}C-NMR (125 MHz, DMSO-d_6) δ: 160.04, 158.19 (2C), 143.09–145.45 (m, 2C), 141.49–143.79 (m, 2C), 131.63 (2C), 125.80, 113.92 (2C), 111.11 (d, J=8.4 Hz, 2C), 79.33, 55.19; ^{19}F-NMR (368 MHz, acetone-d_6) δ: −139.54 (s, 2F), −146.37 (s, 2F); IR (KBr, cm^{-1}) ν: 3513, 3039, 2984, 2850, 1736, 1610, 1499, 1406, 1254, 1154, 942, 860, 733; LR-MS (ESI): m/z 378 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{16}H_9F_4NO_4Na$ $[M+Na]^+$ 378.0360. Found 378.0345.



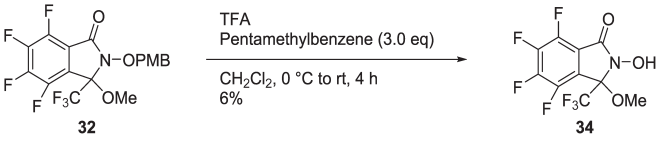
4,5,6,7-Tetrafluoro-3-hydroxy-2-(4-methoxybenzyloxy)-3-trifluoromethylisoindolin-1-one (**31**)

According to the procedure described for the preparation of alcohol **14a** and **b** from phthalimide **13**, the phthalimide **30** (1.29 g, 3.63 mmol) was converted into alcohol **31** (1.43 g, 93%). White powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 7.46 (d, J=8.5 Hz, 2H), 6.96 (d, J=8.5 Hz, 2H), 5.22 (d, J=9.4 Hz, 1H), 5.12 (d, J=9.4 Hz, 1H), 3.81 (s, 3H); ^{13}C-NMR (125 MHz, acetone-d_6) δ: 161.32, 159.48, 145.46 (ddd, J=259.1, 15.6, 15.6 Hz), 144.65 (dd, J=260.3, 12.0 Hz), 144.62 (dd, J=260.3, 12.0 Hz), 143.97 (ddd, J=257.9, 13.2, 13.2 Hz), 132.17 (2C), 127.47, 123.13 (q, J=286.7 Hz), 120.29 (d, J=13.2 Hz), 114.60 (2C), 113.67 (d, J=12.0 Hz), 87.65 (q, J=34.8 Hz), 80.75, 55.54; ^{19}F-NMR (368 MHz, acetone-d_6) δ: −79.03 (s, 3F), −139.73 (s, 1F), −142.66 (s, 1F), −148.13 (s, 1F), −150.75 (s, 1F); IR (KBr, cm^{-1}) ν: 3255, 3010, 2970, 2943, 2843, 1560, 1613, 1519, 1254, 1181, 978, 904, 823, 730; LR-MS (ESI): m/z 448 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{17}H_{10}F_7NO_4Na$ $[M+Na]^+$ 448.0390. Found 448.0368.



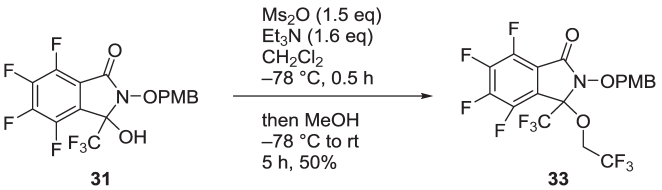
4,5,6,7-Tetrafluoro-3-methoxy-2-(4-methoxybenzyloxy)-3-trifluoromethylisoindolin-1-one (**32**)

To a solution of Ms_2O (110 mg, 0.635 mmol) in CH_2Cl_2 (1.0 mL), a solution of alcohol **31** (180 mg, 0.423 mmol) and Et_3N (94 μL, 0.677 mmol) in CH_2Cl_2 (1.0 mL) was added at −78°C, and the mixture was stirred for 0.5 h at the same temperature. To the mixture, MeOH (2.0 mL) was added, and the mixture was stirred for 0.5 h at −78°C, then for 18 h at rt. H_2O was added to the mixture and the whole was extracted with CH_2Cl_2. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified with flash column chromatography (SiO_2, n-hexane–EtOAc=9 : 1) to afford ether **32** (100 mg, 54%). White powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.43 (d, J=9.0 Hz, 2H), 6.90 (d, J=9.0 Hz, 2H), 5.18 (d, J=9.9 Hz, 1H), 5.05 (d, J=9.9 Hz, 1H), 3.80 (s, 3H), 3.12 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 160.35, 159.91, 144.58 (dddd, J=264.0, 14.1, 14.1, 1.9 Hz), 144.13 (ddd, J=266.9, 12.2, 1.9 Hz), 141.82–144.94 (m, 2C), 131.28 (2C), 126.18, 121.29 (q, J=286.6 Hz), 115.81 (dd, J=13.2, 2.8 Hz), 113.89 (2C), 113.48 (q, J=12.2, 2.8 Hz), 91.40 (q, J=35.7 Hz), 79.21, 55.26, 52.16; ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −77.21 (3F), −136.30 (1F), −137.66 (1F), −143.80 (1F), 146.03 (1F); IR (KBr, cm^{-1}) ν: 3503, 2959, 2846, 1766, 1613, 1505, 1391, 1206, 1029, 914, 733; LR-MS (ESI): m/z 462 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{18}H_{12}F_7NO_4Na$ $[M+Na]^+$ 462.0547. Found 462.0558.



4,5,6,7-Tetrafluoro-2-hydroxy-3-methoxy-3-trifluoromethylisoindolin-1-one (**34**)

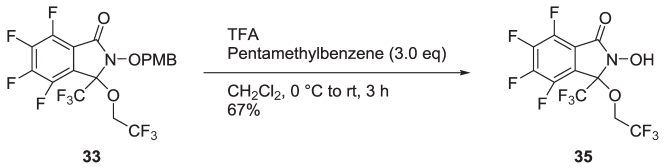
According to the procedure described for the preparation of N-oxyl **28** from PMBether **27**, PMBether **32** (30.0 mg, 0.0591 mmol) was converted into **34** (1.3 mg, 6%). White powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 3.31 (s, 3H); ^{13}C-NMR (100 MHz, acetone-d_6) δ: 159.39, 142.83–146.66 (m, 4C), 122.64 (q, J=287.5 Hz), 116.57 (d, J=11.3 Hz), 114.91 (d, J=10.3 Hz), 91.71 (q, J=32.0 Hz), 52.52; ^{19}F-NMR (368 MHz, acetone-d_6) δ: −78.04 (s, 3F), −139.84 (s, 1F), −142.44 (s, 1F), −148.50 (s, 1F), −150.57 (s, 1F); IR (KBr, cm^{-1}) ν: 3434, 2935, 1735, 1508, 1198, 1109, 918, 803, 731; LR-MS (ESI): m/z 318 $[M-H]^-$; HR-MS (ESI): m/z Calcd for $C_{10}H_3F_7NO_3$ $[M-H]^-$ 318.0007. Found 318.0021.



4,5,6,7-Tetrafluoro-2-(4-methoxybenzyloxy)-3-(2,2,2-trifluoroethoxy)-3-trifluoromethylisoindolin-1-one (**33**)

According to the procedure described for the preparation of ether **32** from alcohol **31** in which 2,2,2-trifluoroenthanol was used as the alcohol instead, alcohol **31** (1.00 g, 2.35 mmol) was converted into ether **33** (0.593 g, 50%). White powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 7.47 (d, J=8.5 Hz, 2H), 6.98 (d, J=8.5 Hz, 2H), 5.20 (s, 2H), 4.17–4.30 (m, 1H), 4.05–4.17 (m, 1H), 3.82 (s, 3H); ^{13}C-NMR (100 MHz, DMSO-d_6) δ: 160.04, 159.39, 141.90–146.29 (m, 4C), 131.16 (2C), 128.59 (d, J=195.4 Hz), 125.93, 123.38 (q, J=279.2 Hz), 120.93 (q, J=286.6 Hz), 114.04 (2C), 113.20 (ddd, J=78.0, 12.2, 2.8 Hz), 90.24 (q, J=34.8 Hz), 79.36, 61.87 (q, J=35.7 Hz), 55.18; ^{19}F-NMR (368 MHz, acetone-d_6) δ: −74.48 (s, 3F), −77.29 (s, 3F), −137.71 (s, 1F), −140.71 (s, 1F), −145.83 (s, 1F), −149.04 (s, 1F); IR (KBr, cm^{-1}) ν: 3435, 2967, 2851, 1750, 1615, 1516, 1290, 1175, 1032, 997, 917, 731; LR-MS (ESI): m/z 530 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{19}H_{11}F_{10}NO_4Na$

$[M+Na]^+$ 530.0421. Found 530.0434.

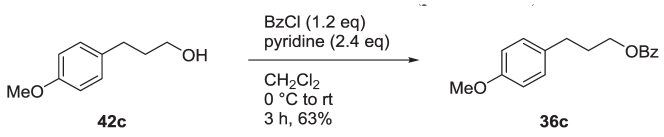


4,5,6,7-Tetrafluoro-2-hydroxy-3-(2,2,2-trifluoroethoxy)-3-trifluoromethylisoindolin-1-one (**35**)

According to the procedure with that described for the preparation of **28** from PMBether **27**, PMBether **33** (53.0 mg, 0.104 mmol) was converted into **35** (26.8 mg, 67%). White powder; ^{1}H-NMR (400 MHz, acetone-d_6) δ: 4.17–4.29 (m, 1H), 4.00–4.11 (m, 1H); ^{13}C-NMR (100 MHz, acetone-d_6) δ: 159.46, 145.78 (ddd, J=259.3, 13.9, 13.9 Hz), 143.23–146.48 (m, 3C), 124.29 (q, J=275.3 Hz), 122.29 (q, J=284.8 Hz), 115.64 (d, J=11.2 Hz), 114.82 (q, J=12.2 Hz), 91.09 (q, J=34.8 Hz), 62.76 (q, J=36.6 Hz); ^{19}F-NMR (368 MHz, acetone-d_6) δ: −74.77 (s, 3F), −77.64 (s, 3F), −138.55 (s, 1F), −141.89 (s, 1F), −147.54 (s, 1F), −149.86 (s, 1F); IR (KBr, cm^{-1}) ν: 3425, 3126, 2926, 1722, 1519, 1502, 1410, 1297, 1173, 927, 807, 733; LR-MS (ESI): m/z 386 $[M-H]^-$; HR-MS (ESI): m/z Calcd for $C_{11}H_2F_{10}NO_3$ $[M-H]^-$ 385.9880. Found 385.9882.

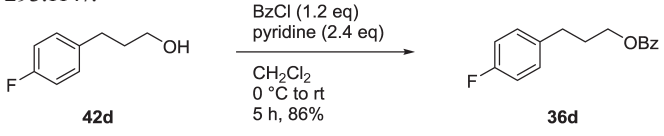
Preparation of Substrates for Aerobic Benzylic C–H Oxidation Full spectroscopic data were described for new compounds. Compound **36a**,[35] **b**,[36] **g**,[37] **h**,[38] **j**,[39] and **k**[40] were prepared following the reported procedures.

General Procedure for Benzoate from Alcohol (Procedure C)



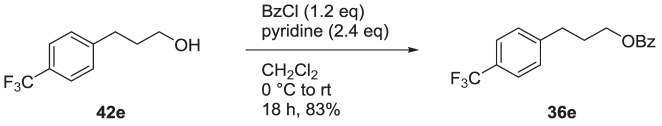
3-(4-Methoxyphenyl)propyl Benzoate (**36c**)

To a solution of 3-(4-methoxyphenyl)-1-propanol **42c** (1.66 g, 10.0 mmol) in CH_2Cl_2 (20 mL), BzCl (1.39 mL, 12.0 mol) and pyridine (1.93 mL, 24.0 mmmol) were added at 0°C. The reaction mixture was stirred for 1 h at the same temperature, and for 2 h at rt. The mixture was cooled to 0°C, and sat. $NaHCO_3$ aq. was added. The phases were separated. The organic layer was washed with H_2O, 1 N HCl aq., H_2O, and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified with flash column chromatography (SiO_2, n-hexane–EtOAc=19 : 1→9 : 1) to afford benzoate **36c** (1.69 g, 63%). Colorless oil ; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.02 (d, J=7.5 Hz, 2H), 7.55 (dd, J=7.5, 7.5 Hz, 1H), 7.43 (dd, J=7.5, 7.5 Hz, 2H), 7.12 (d, J=8.6 Hz, 2H), 6.82 (d, J=8.6 Hz, 2H), 4.31 (t, J=7.5 Hz, 2H), 3.77 (s, 3H), 2.72 (t, J=7.5 Hz, 2H), 2.05 (tt, J=7.5, 7.5 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.36, 157.74, 132.99, 132.69, 130.21, 129.36 (2C), 129.15 (2C), 128.16 (2C), 113.69 (2C), 64.06, 54.99, 31.18, 30.32; IR (neat, cm^{-1}) ν: 3434, 1716, 1637, 1513, 1274, 1116, 711; LR-MS (ESI): m/z 293 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{17}H_{18}O_3Na$ $[M+Na]^+$ 293.1148. Found 293.1147.



3-(4-Fluorophenyl)propyl Benzoate (**36d**)

According to the procedure C, 3-(4-fluorophenyl)-1-propanol **42d** (1.34 g, 8.89 mmol) was converted into benzoate **36d** (1.97 g, 86%). Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.01 (dd, J=7.5. 1.2 Hz, 2H), 7.55 (dd, J=7.5, 7.5 Hz, 1H), 7.43 (dd, J=7.5, 7.5 Hz, 2H), 7.15 (dd, J=8.6, 5.3 Hz, 2H), 6.96 (dd, J=10.9, 10.9 Hz, 2H), 4.32 (t, J=6.9 Hz, 2H), 2.75 (t, J=8.1 Hz, 2H), 2.06 (tt, J=7.5, 6.9 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.33, 161.19 (d, J=243.4 Hz), 136.63 (d, J=14.3 Hz), 132.76, 129.86 (d, J=55.4 Hz), 129.51 (d, J=28.2 Hz), 128.20, 115.12, 114.91, 63.90, 31.31, 30.21; ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −117.79 (s, 1F); IR (neat, cm^{-1}) ν: 3421, 1717, 1644, 1509, 1274, 1221, 1116, 711; LR-MS (ESI): m/z 281 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{16}H_{15}FO_2Na$ $[M+Na]^+$ 281.0948. Found 281.0960.

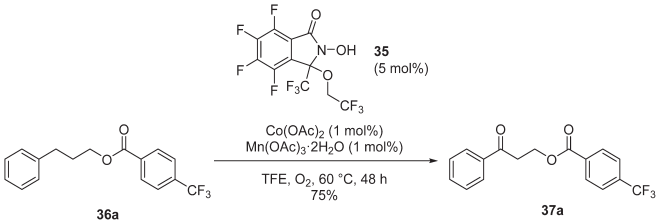


3-(4-Trifluoromethylphenyl)propyl Benzoate (**36e**)

According to the procedure C, 3-(4-trifluoromethylphenyl)-1-propanol **42e** (1.59 g, 7.79 mmol) was converted into benzoate **36e** (1.99 g, 83%). Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.98 (d, J=8.1 Hz, 2H), 7.51–7.58 (m, 3H), 7.43 (dd, J=7.5, 7.5 Hz, 2H), 7.31 (d, J=8.0 Hz, 2H), 4.33 (t, J=6.3 Hz, 2H), 2.84 (t, J=7.5 Hz, 2H), 2.11 (tt, J=6.9, 6.9 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.28, 145.26, 132.78, 130.04, 129.32 (2C), 128.58 (2C), 128.18, 128.17 (q, J=32.0 Hz, 2C), 125.17 (q, J=3.8 Hz, 2C), 124.21 (q, J=271.6 Hz), 63.83, 32.05, 29.75; ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −62.69 (s, 3F); IR (neat, cm^{-1}) ν: 3431, 1643, 1327, 1274, 1118, 1067, 708; LR-MS (ESI): m/z 331 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{17}H_{15}F_3O_2Na$ $[M+Na]^+$ 331.0916. Found 331.0908.

Aerobic Benzylic C–H Oxidation, Etherification, and Acetamidation Full spectroscopic data were described for new compounds. Compound **37b**,[41] **f**,[42] **g**,[43] **h**,[44] **i**,[45] **j**,[46] **l**,[47] **m**,[48] and **n**[49] are known compounds.

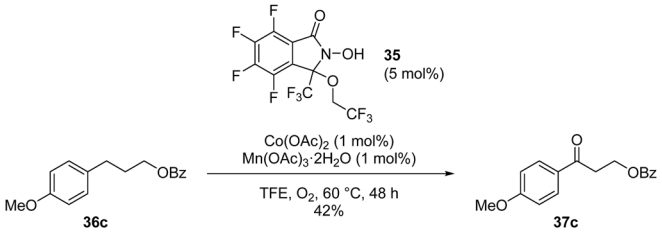
General Procedure for the Oxidation of Benzylic C–H (Procedure D)



3-Oxo-3-phenylpropyl 4-trifluoromethylbenzoate (**37a**)

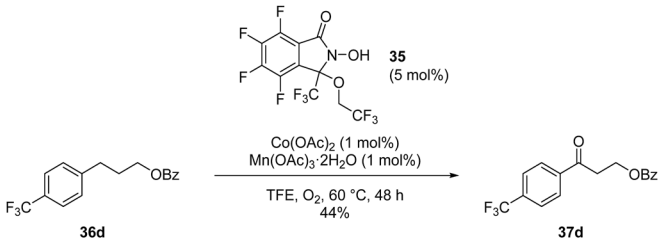
To a solution of benzoate **36a** (72.1 mg, 0.300 mmol) in **35** (5.8 mg, 0.015 mmol), TFE (0.15 mL), $Co(OAc)_2$ (0.53 mg, 0.00300 mmol) and $Mn(OAc)_3 \cdot H_2O$ (0.80 mg, 0.00300 mmol) were added. The reaction mixture was stirred for 48 h at 60°C under O_2 atmosphere. The mixture was evaporated under reduced pressure, and the residue was purified with flash column chromatography (SiO_2, n-hexane–EtOAc=9 : 1) to afford ketone **37a** (59.8 mg, 75%). White powder; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.08 (d, J=8.6 Hz, 2H), 7.98 (d, J=8.6 Hz, 2H), 7.66 (d, J=8.6 Hz, 2H), 7.58 (dd, J=7.4, 7.4 Hz, 1H), 7.48 (dd, J=8.0 Hz, 2H), 4.80 (t, J=6.3 Hz, 2H), 3.46 (t, J=6.3 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 196.80, 165.31, 136.49, 134.47

(q, J=32.4 Hz, 2C), 133.55, 133.20, 130.01 (2C), 128.76, 128.10 (2C), 125.37 (q, J=4.8 Hz, 2C), 123.58 (q, J=273.5 Hz), 60.77, 37.33; ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −63.46 (s, 3F); IR (KBr, cm^{-1}) ν: 3431, 3072, 2979, 1719, 1683, 1324, 1269, 1169, 1100, 1064, 958, 866, 741; LR-MS (ESI): m/z 345 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{17}H_{13}F_3O_3Na$ $[M+Na]^+$ 345.0709. Found 345.0707.



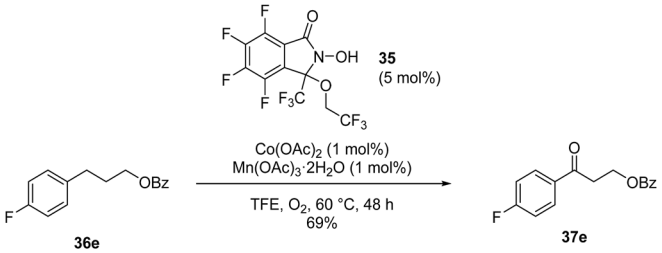
3-(4-Methoxyphenyl)-3-oxopropyl Benzoate (**37c**)

According to the procedure D, benzoate **36c** (81.1 mg, 0.300 mmol) was converted into ketone **37c** (36.0 mg, 42%). Colorless oil; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.93–7.99 (m, 4H), 7.52 (dd, J=7.5, 7.5 Hz, 1H), 7.39 (dd, J=7.4, 7.4 Hz, 2H), 6.93 (d, J=9.2 Hz, 2H), 4.74 (t, J=6.3 Hz, 2H), 3.85 (s, 3H), 3.38 (t, J=6.3 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 195.60, 166.55, 163.71, 132.94 (2C), 130.41, 130.02, 129.74, 129.58 (2C), 128.29 (2C), 113.81 (2C), 60.51, 55.47, 37.16; IR (neat, cm^{-1}) ν: 3433, 1637, 1508, 1458, 1275, 1174, 1110, 669; LR-MS (ESI): m/z 307 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{17}H_{16}O_4Na$ $[M+Na]^+$ 307.0941. Found 307.0929.



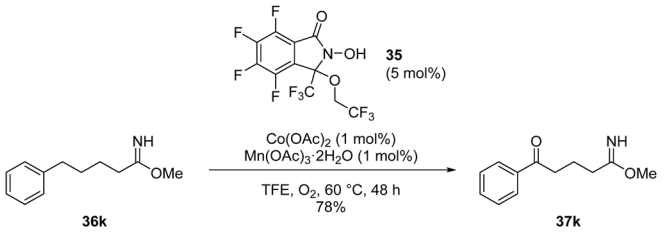
3-Oxo-3-(4-trifluoromethylphenyl)propyl Benzoate (**37d**)

According to the procedure D, benzoate **36d** (92.5 mg, 0.300 mmol) was converted into ketone **37d** (42.6 mg, 44%). White powder; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 8.08 (d, J=8.0 Hz, 2H), 7.96 (d, J=6.9 Hz, 2H), 7.73 (d, J=8.0 Hz, 2H), 7.53 (dd, J=7.5 Hz, 1H), 7.39 (dd, J=7.5, 7.5 Hz, 2H), 4.77 (t, J=6.3 Hz, 2H), 3.47 (t, J=6.3 Hz, 2H); ^{13}C-NMR (125 MHz, $CDCl_3$) δ: 196.16, 166.49, 139.16, 134.71 (q, J=32.4 Hz, 2C), 133.11, 129.82, 129.58, 128.46 (2C), 128.36 (2C), 125.81 (q, J=3.6 Hz, 2C), 123.49 (q, J=272.3 Hz), 59.96, 37.85; ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −63.49 (s, 3F); IR (neat, cm^{-1}) ν: 3412, 3078, 2957, 1716, 1685, 1414, 1322, 1273, 1123, 1065, 857, 710; LR-MS (ESI): m/z 345 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{17}H_{13}F_3O_3Na$ $[M+Na]^+$ 345.0709. Found 345.0705.



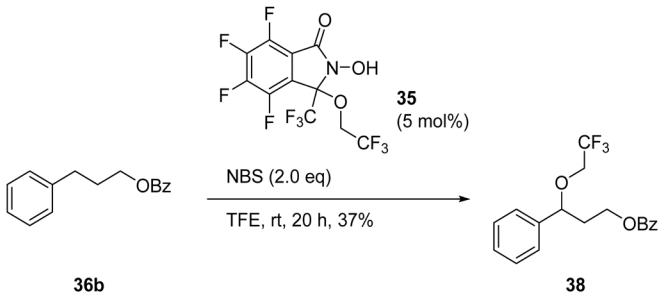
3-(4-Fluorophenyl)-3-oxopropyl Benzoate (**37e**)

According to the procedure D, benzoate **36e** (77.5 mg, 0.300 mmol) was converted into ketone **37e** (56.7 mg, 69%). White powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.95–8.04 (m, 4H), 7.53 (dd, J=7.2, 7.2 Hz, 1H), 7.40 (dd, J=7.6, 7.6 Hz, 2H), 7.13 (dd, J=8.5 Hz, 2H), 4.75 (t, J=6.7 Hz, 2H), 3.41 (t, J=6.7 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 195.43, 166.45, 165.87 (d, J=254.7 Hz), 132.99, 130.73 (d, J=9.4 Hz, 2C), 129.89, 129.53 (2C), 128.29 (2C), 115.78 (d, J=21.6 Hz, 2C), 60.17, 37.39; ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −104.88 (s, 1F); IR (neat, cm^{-1}) ν: 3415, 3072, 2955, 1717, 1677, 1598, 1507, 1332, 1274, 1215, 1120, 976, 850, 713; LR-MS (ESI): m/z 295 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{16}H_{13}FO_3Na$ $[M+Na]^+$ 295.0741. Found 295.0731.



Methyl 5-Oxo-5-phenylpentanimidate (**37k**)

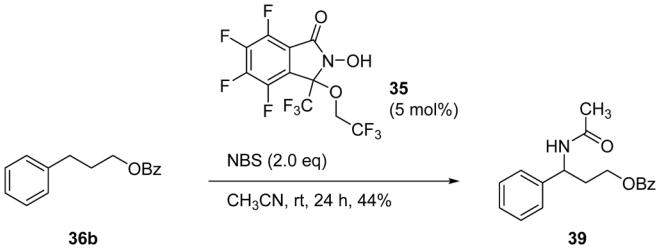
According to the procedure D, benzoate **36k** (17.1 mg, 0.0894 mmol) was converted into ketone **37k** (14.3 mg, 78%). White powder; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.94 (dd, J=9.9, 1.8 Hz, 2H), 7.53 (dd, J=9.0, 9.0 Hz, 1H), 7.44 (dd, J=7.6 Hz, 2H), 3.66 (s, 3H), 3.03 (t, J=7.2 Hz, 2H), 2.43 (t, J=7.2 Hz, 2H), 2.05 (tt, J=7.2, 7.2 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 199.39, 173.72, 136.76, 133.07, 128.58 (2C), 128.00 (2C), 51.57, 37.41, 33.09, 19.29; IR (KBr, cm^{-1}) ν: 3433, 1636, 1563, 1507, 1265, 1101, 664; LR-MS (ESI): m/z 228 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{12}H_{15}NO_2Na$ $[M+Na]^+$ 228.0995. Found 228.1002.



3-Phenyl-3-(2,2,2-trifluoroethoxy)propyl Benzoate (**38**)

To a solution of benzoate **36b** (72.1 mg, 0.300 mmol) in **35** (5.8 mg, 0.015 mmol), TFE (3.0 mL), NBS (106.8 mg, 2.0 eq) was added. The reaction mixture was stirred for 20 h at rt. To the mixture, 10% $Na_2S_2O_3$ aq. was added, and the whole was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified with flash column chromatography (SiO_2, n-hexane–EtOAc=97 : 3→4 : 1) to afford ether **38** (37.3 mg, 37%). Colorless oil; ^{1}H-NMR (400 MHz, $CDCl_3$) δ: 7.94 (d, J=7.2 Hz, 2H), 7.49 (dd, J=7.6, 7.6 Hz, 1H), 7.22–7.40 (m, 7H), 4.55 (dd, J=8.5, 5.4 Hz, 1H), 4.36–4.45 (m, 1H), 4.24–4.34 (m, 1H), 3.50–3.71 (m, 2H), 2.20–2.31 (m, 1H), 2.01–2.12 (m, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 166.41, 139.74, 132.95, 130.17, 129.52 (2C), 128.88

(2C), 128.51, 128.35 (2C), 126.61 (2C), 123.99 (q, J=278.1 Hz), 80.49, 65.88 (q, J=33.8 Hz), 61.45, 37.19; ^{19}F-NMR (368 MHz, $CDCl_3$) δ: −74.33 (s, 3F); IR (neat, cm^{-1}) ν: 3427, 1723, 1634, 1446, 1274, 1117, 1071, 798; LR-MS (ESI): m/z 361 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{18}H_{17}F_3O_3Na$ $[M+Na]^+$ 361.1022. Found 361.1019.



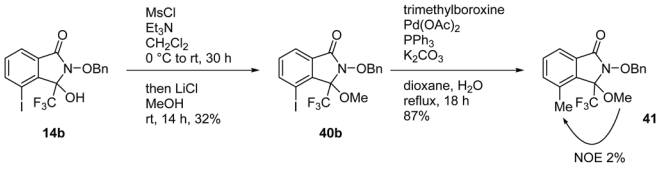
3-Acetamido-3-phenylpropyl Benzoate (**39**)

To a solution of benzoate **36b** (72.1 mg, 0.300 mmol) **35** (5.8 mg, 0.015 mmol) in CH_3CN (3.0 mL), NBS (106.8 mg, 2.0 eq) was added. The reaction mixture was stirred for 24 h at rt. To the mixture, 10% $Na_2S_2O_3$ aq. was added, and the whole was extracted with EtOAc. The organic layer was washed with H_2O and brine, dried over Na_2SO_4, filtered, and evaporated under reduced pressure. The residue was purified with preparative TLC (SiO_2, n-hexane–EtOAc=4 : 1) to afford ether **39** (38.9 mg, 44%). White powder; ^{1}H-NMR (500 MHz, $CDCl_3$) δ: 7.96 (d, J=8.6 Hz, 2H), 7.54 (dd, J=8.1, 8.1 Hz, 1H), 7.38–7.44 (m, 2H), 7.22–7.35 (m, 5H), 5.97 (br s, 1H), 5.19 (td, J=8.0, 8.0 Hz, 1H), 4.29 (t, J=6.3 Hz, 2H), 2.18–2.36 (m, 2H), 1.96 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ: 169.29, 166.45, 141.13, 133.02, 129.53 (2C), 128.88 (2C), 128.37 (2C), 128.25, 127.70, 126.51 (2C), 61.99, 51.05, 34.86, 23.41; IR (KBr, cm^{-1}) ν: 3277, 3075, 1718, 1653, 1558, 1271, 1115, 714; LR-MS (ESI): m/z 320 $[M+Na]^+$; HR-MS (ESI): m/z Calcd for $C_{18}H_{19}NO_3Na$ $[M+Na]^+$ 320.1257. Found 320.1254.

Conflict of Interest The authors declare no conflict of interest.

References and Notes

1) Newhouse T., Baran P. S., *Angew. Chem. Int. Ed.*, **50**, 3362–3374 (2011).
2) White M. C., *Science*, **335**, 807–809 (2012).
3) Roduner E., Kaim W., Sarkar B., Urlacher V. B., Pleiss J., Gläser R., Einicke W.-D., Sprenger G. A., Beifuß U., Klemm E., Liebner C., Hieronymus H., Hsu S.-F., Plietker B. P., Laschat S., *ChemCatChem*, **5**, 82–112 (2013).
4) Chen K., Zhang P., Wang Y., Li H., *Green Chem.*, **16**, 2344–2374 (2014).
5) Ishii Y., Sakaguchi S., Iwahama T., *Adv. Synth. Catal.*, **343**, 393–427 (2001).
6) Recupero F., Punta C., *Chem. Rev.*, **107**, 3800–3842 (2007).
7) Melone L., Punta C., *Beilstein J. Org. Chem.*, **9**, 1296–1310 (2013).
8) Ueda C., Noyama M., Ohmori H., Masui M., *Chem. Pharm. Bull.*, **35**, 1372–1377 (1987).
9) Koshino N., Saha B., Espenson J. H., *J. Org. Chem.*, **68**, 9364–9370 (2003).
10) Sawatari N., Yokota T., Sakaguchi S., Ishii Y., *J. Org. Chem.*, **66**, 7889–7891 (2001).
11) Guha S. K., Obora Y., Ishihara D., Matsubara H., Ryu I., Ishii Y., *Adv. Synth. Catal.*, **350**, 1323–1330 (2008).
12) Nechab M., Einhorn C., Einhorn J., *Chem. Commun.*, **2004**, 1500–1501 (2004).
13) Michaux J., Bessières B., Einhorn J., *Tetrahedron Lett.*, **53**, 48–50 (2012).
14) Zhang Q., Chen C., Ma H., Miao H., Zhang W., Sun Z., Xu J., *J. Chem. Technol. Biotechnol.*, **83**, 1364–1369 (2008).
15) Amorati R., Lucarini M., Mugnaini V., Pedulli G. F., Minisci F., Recupero F., Fontana F., Astolfi P., Greci L., *J. Org. Chem.*, **68**, 1747–1754 (2003).
16) Ozawa J., Tashiro M., Ni J., Oisaki K., Kanai M., *Chem. Sci.*, **7**, 1904–1909 (2016).
17) Prakash G. K. S., Yudin A. K., *Chem. Rev.*, **97**, 757–786 (1997).
18) Regioisomers **14a** and **b**, obtained after the trifluoromethylation of **13**, were characterized by the conversion of **14b** into **41**, whose structure was determined by nuclear Overhauser effect (NOE) analysis. The structure of **14a** was subsequently deduced from the structure of **14b**.



19) Tomashenko O. A., Escudero-Adán E. C., Martínez Belmonte M., Grushin V. V., *Angew. Chem. Int. Ed.*, **50**, 7655–7659 (2011).
20) Jacq J., Berthiol F., Einhorn C., Einhorn J., *Synlett*, **15**, 2263–2266 (2010).
21) Yoshino H., Tsuchiya Y., Saito I., Tsujii M., *Chem. Pharm. Bull.*, **35**, 3438–3441 (1987).
22) Coe P. L., Croll B. T., Patrick C. R., *Tetrahedron*, **23**, 505–508 (1967).
23) Sonobe T., Oisaki T., Kanai M., *Chem. Sci.*, **3**, 3249–3255 (2012).
24) Seki Y., Tanabe K., Sasaki D., Sohma Y., Oisaki K., Kanai M., *Angew. Chem. Int. Ed.*, **53**, 6501–6505 (2014).
25) Kadoh Y., Tashiro M., Oisaki K., Kanai M., *Adv. Synth. Catal.*, **357**, 2193–2198 (2015).
26) Li J., Zhang X., Shen H., Liu Q., Pan J., Hu W., Xiong Y., Chen C., *Adv. Synth. Catal.*, **357**, 3115–3120 (2015).
27) Roberts J. C., Pincock J. A., *Can. J. Chem.*, **81**, 709–722 (2003).
28) Rothenberg M. E., Richard J. P., Jencks W. P., *J. Am. Chem. Soc.*, **107**, 1340–1346 (1985).
29) When **1** was used as the catalyst instead of **35**, 82% (^{1}H-NMR yield) and 54% (^{1}H-NMR yield) were observed for the trifluoroetherification and the acetoamidation, respectively.
30) Michaudel Q., Thevenet D., Baran P. S., *J. Am. Chem. Soc.*, **134**, 2547–2550 (2012).
31) Nair V., Suja T. D., Mohanan K., *Tetrahedron Lett.*, **46**, 3217–3219 (2005).
32) Sakaguchi S., Hirabayashi T., Ishii Y., *Chem. Commun.*, **2002**, 516–517 (2002).
33) Kotani E., Kobayashi S., Ishii Y., Tobinaga S., *Chem. Pharm. Bull.*, **32**, 4281–4291 (1984).
34) Annunziatini C., Gerini M. F., Lanzalunga O., Lucarini M., *J. Org. Chem.*, **69**, 3431–3438 (2004).
35) Shiina I., Kubota M., Oshiumi H., Hashizume M., *J. Org. Chem.*, **69**, 1822–1830 (2004).
36) Sano T., Ohashi K., Oriyama T., *Synthesis*, **1999**, 1141–1144 (1999).
37) Kainmüller E. K., Bannwarth W., *Helv. Chim. Acta*, **89**, 3056–3070 (2006).
38) Yoshimura A., Middleton K. R., Luedtke M. W., Zhu C., Zhdankin V. V., *J. Org. Chem.*, **77**, 11399–11404 (2012).
39) Iida S., Ohmura R., Togo H., *Tetrahedron*, **65**, 6257–6262 (2009).
40) Detert H., Hagelüken A., Seifert R., Schunack W., *Eur. J. Med. Chem.*, **30**, 271–276 (1995).
41) Beets M. G. J., Heeringa L. G., *Recl. Trav. Chim. Pays Bas*, **74**, 1085–1099 (1955).
42) Tyagi V., Gupta A. K., *Synth. Commun.*, **42**, 843–848 (2012).
43) Kamijo S., Amaoka Y., Inoue M., *Chem. Asian J.*, **5**, 486–489

(2010).
44) Cotarca L., Delogu P., Nardelli A., Maggioni P., Bianchini R., Sguassero S., Alini S., Dario R., Clauti G., Pitta G., Duse G., Goffredi F., *Org. Process Res. Dev.*, **5**, 69–76 (2001).
45) Casey B. M., Eakin C. A., Flowers R. A. II, *Tetrahedron Lett.*, **50**, 1264–1266 (2009).
46) Moriyama K., Takemura M., Togo H., *Org. Lett.*, **14**, 2414–2417 (2012).
47) Meng L., Su J., Zha Z., Zhang L., Zhang Z., Wang Z., *Chem. Eur. J.*, **19**, 5542–5545 (2013).
48) Hu J., Adogla E. A., Ju Y., Fan D., Wang Q., *Chem. Commun.*, **48**, 11256–11258 (2012).
49) Kumar R. A., Maheswari C. U., Ghantasala S., Jyothi C., Reddy K. R., *Adv. Synth. Catal.*, **353**, 401–410 (2011).