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Trihaloacetaldehyde *N*,*O*-acetals: useful building blocks for dihalomethylene compounds

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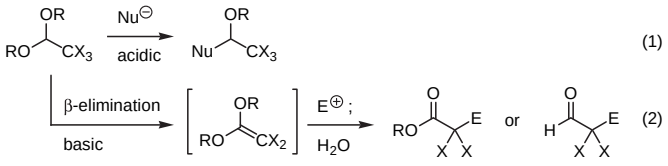
ABSTRACT

The reaction of trifluoroacetaldehyde *N*,*O*-acetals with more than 2 equiv of alkyllithiums at −78 °C resulted in regiospecific defluorinative alkylation with unusual regioselectivity to give α,α-difluoroketone *N*,*O*-acetals in excellent yield. In contrast, under similar conditions, trichloroacetaldehyde *N*,*O*-acetals gave simple mono-dechlorinated product without the alkyl transfer reaction from alkyllithiums to the generated intermediates.

1. Introduction

Halogen-containing organic compounds are significantly interesting in the fields of material sciences and of medicinal chemistry, because introduction of some halogen atoms to organic molecules often results in dramatic change of physicochemical and/or pharmacological properties of the corresponding non-halogenated compounds.[1] Especially, dihalomethylene structures are widely used as key functionalities for the design of biologically active molecules. For example, difluoromethylene group is well recognized as a bioisosteric structure for hydroxymethylene group[2] or ethereal oxygen.[3] Since α,α-difluorinated ketones easily form stable tetrahedral hydrates, these compounds are also used as transition state mimic toward several hydrolases, such as HIV protease,[4] elastase,[5] renin,[6] and human heart chymase.[7] In addition, biologically active natural products having dichloromethylene[8] or dichloromethyl functionalities[9] were recently isolated. For these reasons, the development of effective construction methods for difluoromethylene and dichloromethylene compounds is an important task in synthetic organic chemistry.

To synthesize polyhalogenated compounds, trihaloacetaldehyde derivatives are widely used as readily available halogen-containing synthones. Due to the strong −I effect of trihalomethyl group, these compounds have highly reactive carbonyl group and a wide range of synthetic reactions with nucleophiles has been known.[10] As synthetic equivalents of trihaloacetaldehydes, their acetals and related compounds have also been used.[11] With these types of compounds, not only substitution reaction at the acetalic carbon using various nucleophiles in the presence of acid catalysts but also the use of dihaloketene acetal intermediates as nucleophiles, which generated by base-induced β-elimination of halide, have been realized (Eqs. 1 and 2).[12,13]



As an interesting synthetic application of trihaloacetaldehyde aminal, Dolbier and co-workers reported that the reaction of trifluoroacetaldehyde aminal [$CF_3CH(NMe_2)_2$] with strongly basic *n*-butyllithium (*n*-BuLi) gives difluoroketene aminal through β-elimination of fluoride (Eq. 3).[14,15] Furthermore, the reaction of the resultant ketene aminal with another 1 M equivalent of *n*-BuLi results in regioselective butyl transfer toward electronically more negative α-carbon of fluorine groups and the following β-elimination of fluoride to give the butylated α-monofluoroamide in good yield after acidic aqueous workup.

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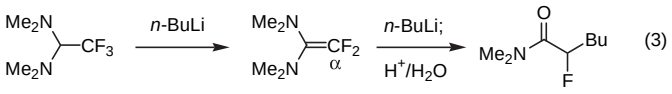


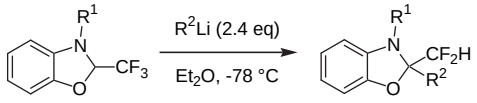
(3)

However, to the best of our knowledge, the synthetic utility of mixed acetals, e.g., *N*,*O*-acetal derivatives, derived from polyhalogenated aldehydes have been limited.[16,17] Therefore, we examined the reaction of trifluoro- and trichloroacetaldehyde *N*,*O*-acetals, and alkyllithiums.[18] In this paper, we disclose the full detail on our work in this area. We found that the reaction of trifluoroacetaldehyde *N*,*O*-acetals with more than 2 equiv of alkyllithium proceeds via β-elimination of fluoride by 1 equiv of alkyllithium followed by alkyl transfer from an excess amount of alkyllithium to the resultant ketene *N*,*O*-acetal intermediates. Observed regioselectivity in alkyl transfer step is different from that of the symmetric aminal. Meanwhile, under similar conditions, an exclusive dechlorination without alkyl transfer by alkyllithium was observed in the case of trichloroacetaldehyde *N*,*O*-acetals. In addition, we applied these dehalogenation reactions to construct α,α-difluoro-β-hydroxyketone *N*,*O*-acetals.

2. Results and discussion

To reveal the regioselectivity in defluorinative alkylation of trifluoroacetaldehyde *N*,*O*-acetal, we examined the reaction of *N*,*O*-acetal **1** with 2.4 equiv of alkyllithiums. Results are summarized in Table 1. The reaction of *N*-allyl substrate **1a** with *n*-BuLi in Et_2O at −78 °C gave difluoromethylketone *N*,*O*-acetal **2aa** as a sole product

Table 1
Defluorinative alkylation of trifluoroacetaldehyde *N*,*O*-acetal **1**

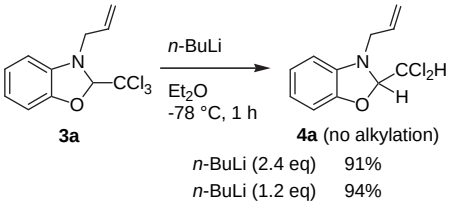


Entry	1	R^1	R^2Li	time (h)	2	Yield[a] (%)
1	**1a**	allyl	*n*-BuLi	3	**2aa**	83
2[b]	**1a**	allyl	MeLi	4	**2ab**	81
3	**1a**	allyl	*c*-C_3H_5Li	4	**2ac**	74
4	**1b**	Bn	*n*-BuLi	5	**2ba**	73
5[c]	**1c**	*n*-C_3H_7	*n*-BuLi	4	**2ca**	58

[a] Isolated yield
[b] Reaction was carried out in Et_2O–THF (2:1) at −24 °C.
[c] Difluoromethylketone of 29% was formed (based in ^{19}F NMR).

in 83% yield.[19] Although the reaction of **1a** with MeLi under the similar conditions resulted in a poor conversion due to low solubility of MeLi in Et_2O, synthetically useful yield of **2ab** was realized by the reaction at −24 °C in Et_2O/THF (2:1 v/v) mixed solvent (entry 2, 81% yield). Cyclopropyllithium was also used as a good alkyl donor for this reaction to result in the clean formation of defluorinative cyclopropylation product **2ac** (entry 3, 74% yield). In contrast, the use of less basic organolithium reagents, such as phenyllithium and allyllithium resulted in no reaction (not shown). These results suggest that the deprotonation at CF_3-substituted methine position is the initiation step for the present reaction. *N*-Benzyl and *N*-propyl substrates **1b**, **c** were also found as nice substrates for this defluorinative alkylation and the corresponding difluoromethylketone *N*,*O*-acetal products **2ba**, **2ca** were obtained in 73% and 58% yield, respectively (entries 4 and 5).

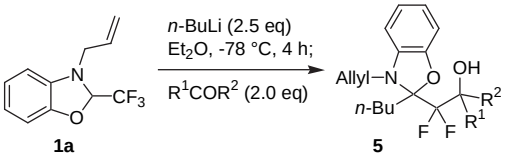
On the other hand, the reaction of trichloroacetaldehyde *N*,*O*-acetal **3a** with 2.4 equiv of *n*-BuLi in Et_2O at −78 °C for 1 h provided the simply dechlorinated product **4a** in 91% yield without the formation of butyl group transfer reaction (Scheme 1). The use of 1.2 equiv of *n*-BuLi gave the essentially same result. This finding strongly suggests that, in the reaction of trichloro substrate, lithium-chlorine exchange is faster than the β-elimination of chloride.



Scheme 1. Dechlorination of trichloroacetaldehyde *N*,*O*-acetal **3a**.

Since it would be expected that the dihalomethyl products **2** and **4** are derived via protonation step during the aqueous workup,[20] we examined the treatment of the intermediates generated by defluorinative alkylation of **1a** with various carbonyls as electrophiles. Results are summarized in Table 2. After the treatment of **1a** with 2.5 M equivalent of *n*-BuLi at −78 °C for 4 h (complete consumption of **1a** was observed in TLC), 2.0 M equivalents of benz-

Table 2
Defluorinative alkylation/Reformatsky type reaction of **1a**, *n*-BuLi and carbonyl electrophiles



Entry	R^1	R^2	Temp. (°C)	Time (h)	5	Yield[a] (%)	dr[b]
1	Ph	H	−78	0.5	**5a**	85	1:1.5
2	4-$MeOC_6H_4$	H	−78	0.5	**5b**	79	1:1.5
3	4-$CF_3C_6H_4$	H	−78	0.5	**5c**	85	1:1.7
4	2-Furyl	H	−78	1	**5d**	87	1.2:1
5	2-Pyridyl	H	−78	0.25	**5e**	87	3.4:1
6	CH=CHPh	H	−78	1	**5f**	87	1:1.2
7	CH_2CH_2Ph	H	−24	3	**5g**	76	11:1[c]
8	*c*-C_6H_{11}	H	0	8	**5h**	81	11:1[c]
9	Me	Me	rt	9	**5i**	89	—
10	$-CH_2(CH_2)_3CH_2$	—	0	6	**5j**	84	—
11	Ph	Me	rt	9	**5k**	79	1.8:1

[a] Isolated yield.
[b] Based on ^{19}F NMR.
[c] *anti*/*syn* Selectivity.

aldehyde was added to the resultant reaction mixture. The reaction of the intermediate with benzaldehyde rapidly completed (within 0.5 h) to give the desired α,α-difluoro-β-hydroxyketone *N*,*O*-acetal **5a** in 85% yield with low diastereoselectivity (entry 1). 4-Substituted benzaldehyde derivatives, such as 4-anisaldehyde and 4-trifluoromethylbenzaldehyde, and furfural also gave the corresponding carbinol **5b**–**d** in excellent yield by the reaction at −78 °C (entries 2–4). Interestingly, in the reaction with 2-pyridinecarbaldehyde, the reaction rate was significantly accelerated under the same conditions and carbinol product **5e** was formed in 87% yield with moderate diastereoselectivity (entry 5). The reaction with cinnamaldehyde proceeded with perfect 1,2-selectivity to give allylic alcohol **5f** in 87% yield (entry 6). In contrast, although somewhat low reactivity of aliphatic aldehydes was observed in this C–C bond forming reaction, reasonable product yield was realized by conducting the reaction at a higher reaction temperature and for a prolonged reaction time (entries 7 and 8). With aliphatic aldehyde examined, the diastereoselectivity was generally high. For example, the reaction with cyclohexanecarbaldehyde smoothly proceeded at 0 °C for 8 h to give carbinol **5h** in 81% yield as a mixture of diastereomers in a ratio of 11:1. The stereochemistry of

the major diastereomer was determined as 1,3-*anti* relationship on the basis of X-ray crystallographic analysis (Fig. 1). In this one-pot procedure to obtain α,α-difluoro-β-hydroxyketone *N*,*O*-acetals, it was also found that ketones perform as nice carbonyl components. After defluorinative alkylation of *N*,*O*-acetal **1a** by *n*-BuLi, the reaction of the resultant intermediate with acetone at room temperature for 9 h gave difluorinated tertiary alcohol **5i** in 89% yield (entry 9). Likewise, the reactions with cyclohexanone and with acetophenone resulted in clean formation of **5j** and **5k** in 84% and 79% yield, respectively (entries 10, 11).

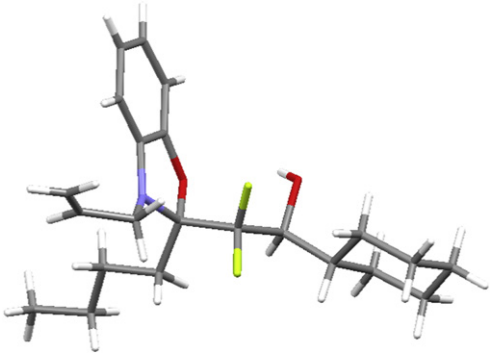
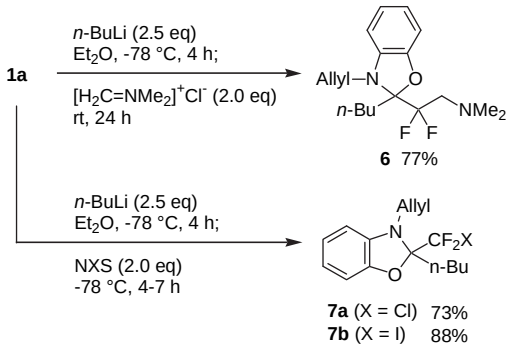


Figure 1. X-ray structure of *anti*-**5h**.

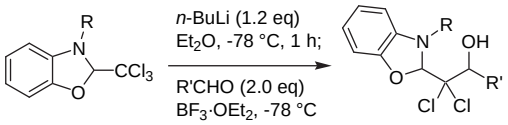
As additional entries of the present defluorinative approach toward difluoromethylene compounds, we carried out the reactions using other electrophiles (Scheme 2). For example, after defluorinative alkylation reaction of **1a** with *n*-BuLi, the one-pot treatment of the resultant mixture by iminium salt at room temperature provided β-amino-α,α-difluoroketone *N*,*O*-acetal product **6** in 77% yield. By using *N*-halosuccinimides (NXS) as electrophiles, the corresponding difluorohalomethylketone *N*,*O*-acetal **7** was also obtained in excellent yields. That is, the one-pot reaction of **1a**, *n*-BuLi and NCS smoothly proceeded at −78 °C to give chlorinated product **7a** in 73% yield. Under similar conditions, the use of NIS resulted in clean formation of difluoroiodomethyl ketone derivative **7b** in 88% isolated yield.



Scheme 2. One-pot synthesis of α,α-difluoroketone *N*,*O*-acetals **6** and **7**.

Next, we turned our attention to examine the C–C bond forming reaction of the intermediate generated by dechlorination of *N*,*O*-acetal **3**. Since dechlorinative addition of masked chloroacetaldehyde to aldehydes should provide an alternative method for the cross Reformatsky type reaction of chloroacetaldehyde derivatives,[21,22] we examined the Reformatsky-type reaction of trichloroacetaldehyde *N*,*O*-acetal **3** by stepwise addition of *n*-BuLi and benzaldehyde (Table 3). Although the intermediate generated by dechlorination of **3a** with 1.2 equiv of *n*-BuLi did not react with benzaldehyde in the absence of catalysts at −78 °C (entry 1), $BF_3{\cdot}OEt_2$ was found as a useful Lewis acid for this reaction. That is, after complete dechlorination of **3a** with *n*-BuLi, the resultant reaction mixture was treated with a 1:1 mixture of benzaldehyde and $BF_3{\cdot}OEt_2$ at −78 °C for 3 h to give the desired dichloromethyl carbinol **8a** in 65% yield (entry 2). The product yield was sensitive to the amount of $BF_3{\cdot}OEt_2$ and excellent yield was realized on using 6.0 equiv of $BF_3{\cdot}OEt_2$ (85% yield, entry 3). Under the same conditions, 2- or 4-bromobenzaldehydes could be used for this reaction giving rise to the corresponding carbinols **8b** and **8c** in 72% and 80% yield, respectively (entries 4 and 5). The reaction with cinnamaldehyde selectively gave 1,2-adduct **8d** in 75% yield with low diastereoselectivity (entry 6). Effect of *N*-substituent of *N*,*O*-acetal **3** on its reactivity was little. For example, reactions of both *N*-benzyl substrate **3b** and *N*-propyl substrate **3c** with 4-bromobenzldehyde smoothly proceeded to give **8e** and **8f** in good yields (entries 7 and 8).

Table 3
n-BuLi-mediated Reformatsky type reaction of trichloroacetaldehyde *N*,*O*-acetal **3**

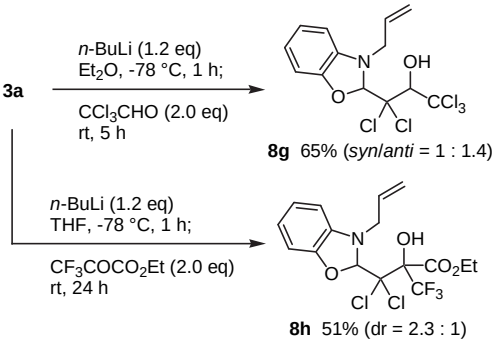


3 **8**

Entry	3	R′	$BF_3{\cdot}OEt_2$ (eq)	Time (h)	8	Yield[a] (%)	dr[b]
1	**3a** (R=allyl)	Ph	None	1	**8a**	0	—
2	**3a** (R=allyl)	Ph	2.0	3	**8a**	65	2.2:1
3	**3a** (R=allyl)	Ph	6.0	1	**8a**	85	2.0:1
4	**3a** (R=allyl)	2-BrC_6H_4	6.0	2	**8b**	72	2.3:1[c]
5	**3a** (R=allyl)	4-BrC_6H_4	6.0	1	**8c**	80	2.2:1
6	**3a** (R=allyl)	CH=CHPh	6.0	1	**8d**	75	1.4:1
7	**3b** (R=Bn)	4-BrC_6H_4	6.0	1	**8e**	78	1.7:1
8	**3c** (R=*n*-Pr)	4-BrC_6H_4	6.0	1	**8f**	72	2.2:1

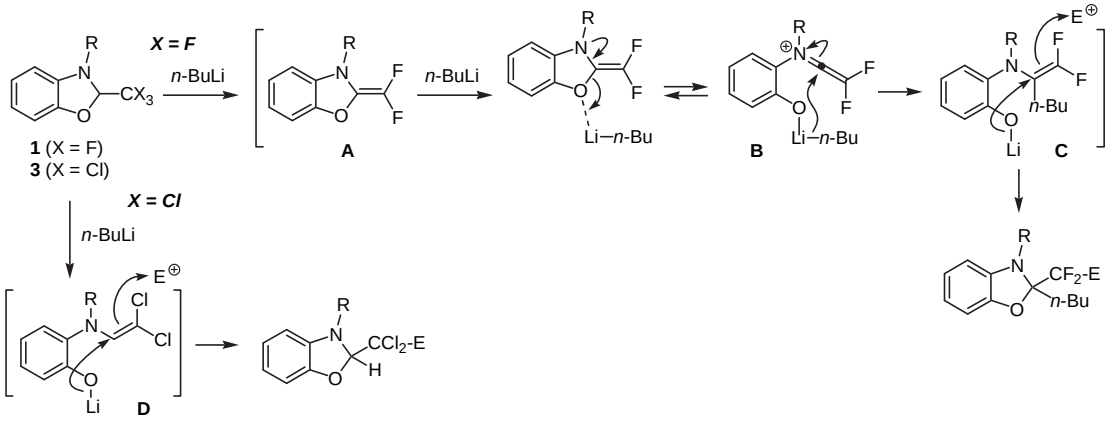
[a] Isolated yirld
[b] Determined by ^1H NMR.
[c] *anti*/*syn* Ratio.

We also found that the use of $BF_3{\cdot}OEt_2$ is not necessary in the reactions with highly electrophilic carbonyls (Scheme 3). For example, *n*-BuLi-mediated reaction of **3a** with chloral proceeded at room temperature in the absence of $BF_3{\cdot}OEt_2$ to give pentachlorinated alcohol **8g** in 65% yield. Furthermore, tertiary alcohol **8h** was obtained in reasonable yield by the reaction of **3a** with ethyl trifluoropyruvate at room temperature for 24 h.



Scheme 3. Reformatsky type reaction of **3a** in the absence of $BF_3{\cdot}OEt_2$.

Concerning these results, we propose the reaction mechanism as shown in Scheme 4. In the case of trifluoroacetaldehyde *N*,*O*-acetal **1**, as the first step, β-elimination of *N*,*O*-acetal **1** by 1 equiv of alkyllithiums rapidly gives difluoroketene *N*,*O*-acetal intermediate **A**.[16,23] Dolbier and co-workers reported that butyl transfer of



Scheme 4. Proposed reaction mechanism.

difluoroketene aminal [$F_2C{=}C(NMe_2)_2$] by *n*-BuLi proceeds at electronically more negative α-position of fluorine atoms to give α-fluoroamide after aqueous workup.[14] In contrast, the structure of the products in this study clearly indicates that alkyl transfer from an excess alkyllithium to the resultant intermediate **A** proceeds at β-position of fluorines. We attributed this unusual regioselectivity to the equilibrium between ketene *N*,*O*-acetal form **C** and zwitterion form **B**. That is, alkyl transfer to **A** by an excess alkyllithium is possibly induced by the coordination of *N*,*O*-acetal oxygen to lithium center to give lithium phenoxide **C** via zwitterion **B**.[24] Protonation of **C** or reaction of **C** with carbonyl electrophiles probably proceeds with the simultaneous formation of dihydrobenzoxazole structure via 5-*exo*-*trig* cyclization. On the other hand, the reaction of trichloroacetaldehyde *N*,*O*-acetal **3** with *n*-BuLi would result in a rapid lithium-chlorine exchange prior to β-elimination of chloride to give enamine phenoxide **D**. Therefore, the following butyl transfer does not occur under the present conditions.

3. Conclusion

We found that the reaction of trifluoroacetaldehyde *N*,*O*-acetal with more than 2 equiv of alkyllithium proceeded via β-elimination of fluoride with 1 equiv of alkyllithium followed by alkyl transfer from an excess amount of alkyllithium to the resultant ketene *N*,*O*-acetal intermediate. Observed regioselectivity in the alkyl transfer step is different from that of difluoroketene aminal with symmetric structure. Under the similar conditions, trichloroacetaldehyde *N*,*O*-acetal provided only dechlorinated intermediate without alkyl transfer by excess alkyllithium. Moreover, we showed that, by the treatment with carbonyl electrophiles, the intermediates derived from the reactions of these *N*,*O*-acetals with alkyllithium can be converted to α,α-dihalo-β-hydroxycarbonyl *N*,*O*-acetals in excellent yields. These findings clearly demonstrate the synthetic utilities of trihaloacetaldehyde *N*,*O*-acetals as dihalomethyl anion precursors through carbon–fluorine or carbon–chlorine bond cleavage.

4. Experimental section

4.1. Preparation of trihaloacetaldehyde *N*,*O*-acetal substrates

*4.1.1. 3-Allyl-2-(trifluoromethyl)-2,3-dihydrobenzo[d]oxazole (**1a**).* To a round-bottom flask equipped with Dean–Stark apparatus, 2-(allylamino)phenol[25] (2.99 g, 20 mmol), TFAE (5.76 g, 40 mmol), *p*-toluenesulfonic acid monohydrate (200 mg, 1.1 mmol), and benzene (150 mL) were added. After being refluxed for 4 h, reaction mixture was quenched with saturated $NaHCO_3$ aqueous solution, extracted with Et_2O (30 mL×3) and evaporated. The resulting residue was purified by column chromatography on silica gel to give **1a** (4.03 g, 17.6 mmol, 88% yield). Pale yellow oil; IR (neat) ν 3064, 2983, 1487, 1291, 1156, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (1H, dd, J=15.8, 6.9 Hz), 3.91 (1H, dd, J=15.8, 5.2 Hz), 5.28 (1H, dd, J=8.7, 1.4 Hz), 5.32 (1H, dd, J=15.6, 1.4 Hz), 5.66 (1H, q, J_{H-F}=4.0 Hz), 5.78–5.89 (1H, m), 6.73 (1H, d, J=7.7 Hz), 6.78–6.83 (2H, m), 6.84–6.91 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 54.2, 92.8 (q, J_{C-F}=35.8 Hz), 108.3, 110.4, 119.3, 121.3, 121.8 (q, J_{C-F}=284.5 Hz), 122.2, 136.1, 138.0, 150.2; ^{19}F NMR (282 Hz, $CDCl_3$) δ −21.3 (3F, d, J_{H-F}=4.0 Hz); MS (ESI-TOF) m/z 230 $[M+H]^+$; HRMS calcd for $C_{11}H_{11}F_3NO$ $[M+H]^+$, 230.0793; found, 230.0804.

*4.1.2. 3-Benzyl-2-(trifluoromethyl)-2,3-dihydrobenzo[d]oxazole (**1b**).* According to the preparation of **1a**, this compound was obtained in 87% yield (3.63 g, 13.0 mmol) from 2-(benzylamino) phenol[26] (2.99 g, 15 mmol) and TFAE (4.33 g, 30 mmol). Pale yellow oil; IR (neat) ν 3065, 2888, 1601, 1488, 1292, 1254, 1153, 739, 697 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.35 (1H, d, J=15.4 Hz), 4.54 (1H, d, J=15.4 Hz), 5.68 (1H, q, J_{H-F}=4.0 Hz), 6.67 (1H, br d, J=6.9 Hz), 6.78–6.88 (3H, m), 7.28–7.40 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 93.0 (q, J_{C-F}=35.8 Hz), 108.3, 110.0, 121.1, 121.8 (q, J_{C-F}=284.3 Hz), 122.2, 127.8, 128.0, 128.8, 136.2, 138.4, 149.9; ^{19}F NMR (282 Hz, $CDCl_3$) δ −20.9 (3F, d, J_{H-F}=4.0 Hz); MS (ESI-TOF) m/z 280 $[M+H]^+$; HRMS calcd for $C_{15}H_{13}F_3NO$ $[M+H]^+$, 280.0949; found, 280.0968.

*4.1.3. 3-Propyl-2-(trifluoromethyl)-2,3-dihydrobenzo[d]oxazole (**1c**).* Under H_2 atmosphere (1 atm), a mixture of 3-allyl-2-(trifluoromethyl)-2,3-dihydro-1,3-benzoxazole **1a** (462.2 mg, 2.0 mmol) and 10% palladium on carbon (50% wet., 212 mg, 0.1 mmol) in EtOAc (5.0 mL) was stirred for 6 h at room temperature. A resulting mixture was filtrated through Celite pad and the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel to give **1c** (450.8 mg, 1.95 mmol, 97% yield). Colorless oil; IR (neat) ν 3063, 2968, 2879, 1489, 1292, 1245, 1154, 1058, 854, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.98 (3H, t, J=7.4 Hz), 1.58–1.74 (2H, m), 3.13–3.26 (2H, m), 5.64 (1H, q, J_{H-F}=4.2 Hz), 6.69 (1H, d, J=7.2 Hz), 6.65–6.83 (2H, m), 6.86–6.91 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.2, 21.2, 54.2, 94.0 (q, J_{C-F}=35.4 Hz), 108.1, 110.0, 120.9, 121.7 (q, J_{C-F}=284.0 Hz), 122.2, 138.7, 150.0; ^{19}F NMR (282 Hz, $CDCl_3$) δ −21.4 (3F, d, J_{H-F}=4.2 Hz); MS (ESI-TOF) m/z 232 $[M+H]^+$; HRMS calcd for $C_{11}H_{13}F_3NO$ $[M+H]^+$, 232.0949; found, 232.0950.

*4.1.4. 3-Allyl-2-(trichloromethyl)-2,3-dihydrobenzo[d]oxazole (**3a**).* To a round-bottom flask equipped with Dean–Stark apparatus, 2-(allylamino)phenol[25] (1.21 g, 8.0 mmol), chloral (2.36 g, 16 mmol), PPTS (50 mg, 0.2 mmol), and benzene (100 mL) were added. After being refluxed for 2 h, reaction mixture was quenched with

saturated $NaHCO_3$ aqueous solution, extracted with Et_2O (30 mL×3) and evaporated. The resulting residue was purified by column chromatography on silica gel to give trichloroacetaldehyde *N*,*O*-acetal **3a** (1.75 g, 6.3 mmol, 79% yield). Pale yellow oil; IR (neat) ν 3064, 2878, 1487, 1241, 830, 804, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.97 (1H, dd, *J*=16.2, 7.2 Hz), 4.12–4.20 (1H, m), 5.28 (1H, d, *J*=10.3, 1.2 Hz), 5.36 (1H, dd, *J*=17.1, 1.2 Hz), 5.77–5.90 (1H, m), 5.83 (1H, s), 6.76 (1H, d, *J*=7.4 Hz), 6.78–6.90 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0, 100.9, 103.0, 107.8, 110.2, 119.0, 121.3, 122.1, 132.4, 138.9, 150.5; MS (ESI-TOF) *m*/*z* 278 $[M+H]^+$; HRMS calcd for $C_{11}H_{11}Cl_3NO$ $[M+H]^+$, 277.9906; found, 277.9894.

*4.1.5. 3-Benzyl-2-(trichloromethyl)-2,3-dihydrobenzo[d]oxazole (**3b**).* According to the synthetic procedure for **3a**, this compound was obtained in 83% yield (4.06 g, 12.5 mmol) by the reaction of 2-(benzylamino)phenol[26] (2.99 g, 15 mmol), chloral (4.43 g, 30 mmol) in the presence of PPTS (100 mg, 0.4 mmol) in benzene (200 mL). Colorless crystals; mp 84.0–85.5 °C; IR (KBr) ν 3063, 2881, 1487, 1256, 1175, 1009, 831, 801, 763 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 4.54 (1H, d, *J*=15.7 Hz), 4.79 (1H, d, *J*=15.7 Hz), 5.87 (1H, s), 6.52 (1H, dd, *J*=5.6, 3.2 Hz), 6.77–6.89 (3H, m), 7.28–7.39 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.3, 100.8, 103.2, 107.2, 110.1, 121.3, 122.2, 127.5, 127.8, 128.8, 136.7, 139.3, 150.3; MS (EI) *m*/*z* 327 $[M]^+$, 329 $[M+2]^+$, 210 $[M-CCl_3]^+$. Anal. Calcd for $C_{15}H_{12}Cl_3NO$: C, 54.82; H, 3.68; N, 4.26. Found: C, 54.73; H, 3.80; N, 4.33.

*4.1.6. 3-Propyl-2-(trichloromethyl)-2,3-dihydrobenzo[d]oxazole (**3c**).* Under H_2 atmosphere (1 atm), a mixture of 3-allyl-2-(trichloromethyl)-2,3-dihydrobenzo[*d*]oxazole **3a** (0.56 g, 2.0 mmol) and 10% palladium on carbon (50% wet., 420 mg, 0.2 mmol) in EtOAc (5.0 mL) was stirred for 3 h at room temperature. A resulting mixture was filtrated through Celite pad, then the filtrate was concentrated under reduced pressure. The obtained residue was purified by column chromatography on silica gel to give **3c** in 62% yield (347.9 mg, 1.24 mmol). Pale yellow oil; IR (neat) ν 3061, 2965, 2876, 1488, 1268, 1243, 829, 803, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, t, *J*=7.4 Hz), 1.61–1.71 (2H, m), 3.33–3.49 (2H, m), 5.83 (1H, s), 6.72 (1H, d, *J*=7.4 Hz), 6.76–6.84 (2H, m), 6.88 (1H, dt, *J*=7.4, 1.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 11.3, 20.5, 54.9, 101.0, 103.6, 107.7, 109.9, 120.9, 122.0, 138.9, 150.5; MS (ESI-TOF) *m*/*z* 280 $[M+H]^+$; HRMS calcd for $C_{11}H_{13}Cl_3NO$ $[M]^+$, 280.0063; found, 280.0052.

4.2. Regiospecific defluorinative alkylation reaction of trifluoroacetaldehyde *N*,*O*-acetal

*4.2.1. 3-Allyl-2-butyl-2-(difluoromethyl)-2,3-dihydrobenzo[d]oxazole (**2aa**).* To a solution of trifluoroacetaldehyde *N*,*O*-acetal **1a** (114.5 mg, 0.5 mmol) in Et_2O (2.0 mL), *n*-BuLi (1.55 M in hexane, 0.77 mL, 1.2 mmol) was added at −78 °C over 15 min. After being stirred for 4 h at the same temperature, the mixture was poured into ice water and Et_2O, which was extracted with Et_2O (20 mL×3). The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. The obtained residue was purified by short column chromatography on silica gel to give difluoroacetaldehyde *N*,*O*-acetal **2aa** in 83% yield (110.8 mg, 0.42 mmol). Colorless oil; IR (neat) ν 3064, 2959, 2873, 1599, 1456, 1398, 1311, 1235, 1201, 1116, 1073, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J*=7.2 Hz), 1.25–1.59 (4H, m), 1.97 (2H, t, *J*=7.9 Hz), 3.76–3.95 (2H, m), 5.21 (1H, dd, *J*=10.3, 1.5 Hz), 5.33 (1H, dd, *J*=17.2, 1.5 Hz), 5.68 (1H, t, J_{H-F}=55.4 Hz), 5.83–5.94 (1H, m), 6.39 (1H, dd, *J*=7.5, 1.0 Hz), 6.54–6.62 (1H, m), 6.65 (1H, dd, *J*=7.6, 1.0 Hz), 6.70–6.77 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.6, 23.4, 28.8, 46.9, 100.9 (t, J_{C-F}=23.6 Hz), 105.2, 106.8, 114.0 (dd, J_{C-F}=254.8, 251.0 Hz), 116.8, 117.9, 121.6, 133.9, 139.0, 148.9; ^{19}F NMR (282 Hz, $CDCl_3$) δ −71.3 (1F, dd, J_{F-F}=285.4 Hz, J_{H-F}=55.4 Hz), −66.7 (1F, dd, J_{F-F}=285.4 Hz, J_{H-F}=55.4 Hz); MS (ESI-TOF) *m*/*z* 268 $[M+H]^+$; HRMS calcd for $C_{15}H_{20}F_2NO$ $[M+H]^+$, 268.1513; found, 268.1500.

*4.2.2. 3-Allyl-2-(difluoromethyl)-2-methyl-2,3-dihydrobenzo[d]oxazole (**2ab**).* This compound was obtained in 81% yield (91.1 mg, 0.40 mmol) by the reaction of trifluoroacetaldehyde *N*,*O*-acetal **1a** (114.3 mg, 0.5 mmol) and methyllithium (1.09 M in Et_2O, 1.10 mL, 1.2 mmol) in Et_2O/THF (3:1, 4 mL) for 4 h at −24 °C. Brown oil; IR (neat) ν 3064, 2986, 1599, 1494, 1394, 1302, 1227, 1096, 1074, 735 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 1.64 (3H, br s), 3.79 (1H, dd, *J*=16.8, 5.6 Hz), 3.90–3.98 (1H, m), 5.21 (1H, dd, *J*=10.3, 1.5 Hz), 5.31 (1H, dd, *J*=17.1, 1.5 Hz), 5.67 (1H, t, J_{H-F}=55.3 Hz), 5.83–8.94 (1H, m), 6.46 (1H, d, *J*=7.5 Hz), 6.61–6.70 (2H, m), 6.74–6.81 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.7, 47.5, 99.4 (t, J_{C-F}=25.0 Hz), 106.8, 107.5, 113.7 (dd, *J*=254.9, 249.6 Hz), 116.9, 118.7, 121.7, 134.2, 138.4, 148.4; ^{19}F NMR (282 Hz, $CDCl_3$) δ −70.9 (1F, dd, J_{F-F}=287.3 Hz, J_{H-F}=55.3 Hz), −66.8 (1F, dd, J_{F-F}=287.3 Hz, J_{H-F}=55.3 Hz); MS (EI) *m*/*z* 225 $[M]^+$. Anal. Calcd for $C_{12}H_{13}F_2NO$: C, 63.99; H, 5.82; N, 6.22. Found: C, 63.82; H, 5.91; N, 6.40.

*4.2.3. 3-Allyl-2-cyclopropyl-2-(difluoromethyl)-2,3-dihydrobenzo[d]oxazole (**2ac**).* This compound was obtained in 74% yield (92.9 mg, 0.37 mmol) by the reaction of trifluoroacetaldehyde *N*,*O*-acetal **1a** (114.6 mg, 0.5 mmol) and cyclopropyllithium (1.2 M in hexane, 1.0 mL, 1.2 mmol) in Et_2O (2 mL) for 4 h at −78 °C. Pale yellow oil; IR (neat) ν 3064, 3015, 2980, 1599, 1494, 1230, 1074, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.48–0.55 (2H, m), 0.65–0.72 (1H, m), 0.86–0.92 (1H, m), 1.38–1.46 (1H, m), 3.91 (1H, dd, *J*=16.7, 5.4 Hz), 4.14 (1H, dd, *J*=16.7, 5.2 Hz), 5.23 (1H, d, *J*=10.3 Hz), 5.36 (1H, *J*=17.2 Hz), 5.72 (1H, t, J_{H-F}=55.5 Hz), 5.91–6.03 (1H, m), 6.47 (1H, d, *J*=7.6 Hz), 6.58–6.66 (1H, m), 6.76 (1H, t, *J*=7.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ −0.6, 1.8, 9.9, 48.0, 99.2 (t, J_{C-F}=23.7 Hz), 106.26 107.0, 114.1 (dd, J_{C-F}=252.9, 250.9 Hz), 116.6, 118.3, 121.6, 134.6, 139.3, 148.8; ^{19}F NMR (282 Hz, $CDCl_3$) δ −71.8 (1F, dd, J_{F-F}=285.2 Hz, J_{H-F}=55.5 Hz), −67.4 (1F, dd, J_{F-F}=285.2 Hz, J_{H-F}=55.5 Hz); MS (ESI-TOF) *m*/*z* 252 $[M+H]^+$; HRMS calcd for $C_{14}H_{16}F_2NO$ $[M+H]^+$, 252.1200; found, 252.1179.

*4.2.4. 3-Benzyl-2-butyl-2-(difluoromethyl)-2,3-dihydrobenzo[d]oxazole (**2ba**).* This compound was obtained in 73% yield (115.8 mg, 0.37 mmol) by the reaction of trifluoroacetaldehyde *N*,*O*-acetal **1a** (139.8 mg, 0.5 mmol) and *n*-BuLi (1.55 M in hexane, 0.77 mL, 1.2 mmol) in Et_2O (2 mL) for 5 h at −78 °C. Pale yellow crystals; mp 62.5–63.0 °C; IR (KBr) ν 3063, 2959, 2872, 1645, 1600, 1494, 1235, 1074, 732, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.93(3H, t, *J*=7.1 Hz), 1.29–1.44 (3H, m), 1.52–1.61 (1H, m), 2.01–2.07 (2H, m), 4.43 (1H, d, *J*=16.1 Hz), 4.54 (1H, d, *J*=16.1 Hz), 5.78 (1H, t, J_{H-F}=55.3 Hz), 6.12 (1H, d, *J*=7.3 Hz), 6.59–6.73 (3H, m), 7.27–7.43 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.7, 23.6, 295, 48.7, 101.2 (t, J_{C-F}=23.3 Hz), 106.0, 106.9, 114.3 (dd, J_{C-F}=254.5, 251.5 Hz), 118.4, 121.6, 126.8, 127.3, 128.7, 137.7, 139.4, 149.0; ^{19}F NMR (282 Hz, $CDCl_3$) δ −71.0 (1F, dd, J_{F-F}=285.4 Hz, J_{H-F}=55.3 Hz), −66.4 (1F, dd, J_{F-F}=285.4 Hz, J_{H-F}=55.3 Hz); MS (EI) *m*/*z* 317 $[M]^+$, 266 $[M-CHF_2]^+$. Anal. Calcd for $C_{19}H_{21}F_2NO$: C, 71.90; H, 6.67; N, 4.41. Found: C, 72.03; H, 6.80; N, 4.41.

*4.2.5. 2-Butyl-2-(difluoromethyl)-3-propyl-2,3-dihydrobenzo[d]oxazole (**2ca**).* This compound was obtained in 58% yield (78.1 mg, 0.29 mmol) by the reaction of trifluoroacetaldehyde *N*,*O*-acetal **1a** (115.4 mg, 0.5 mmol) and *n*-BuLi (1.55 M in hexane, 0.77 mL, 1.2 mmol) in Et_2O (2 mL) for 4 h at −78 °C. Colorless oil; IR (neat) ν 3062, 2962, 2874, 1599, 1496, 1235, 1116, 1072, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J*=7.3 Hz), 0.97 (3H, t, *J*=7.4 Hz), 1.21–1.53 (4H, m), 1.62–1.80 (2H, m), 1.93–2.00 (2H, m), 3.16 (2H, t, *J*=7.8 Hz), 5.67 (1H, t, J_{H-F}=55.5 Hz), 6.37 (1H, dd, *J*=7.5, 1.0 Hz), 6.54–6.60 (1H, m), 6.64 (1H, dd, *J*=7.6, 1.0 Hz), 6.71–6.79 (1H, m);

^{13}C NMR (100 MHz, $CDCl_3$) δ 11.4, 13.9, 22.2, 22.7, 23.9, 46.3, 101.0 (t, J_{C-F}=23.7 Hz), 104.2, 106.7, 114.1 (dd, J_{C-F}=254.8, 251.0 Hz), 117.4, 121.6, 139.6, 148.9; ^{19}F NMR (282 Hz, $CDCl_3$) δ −71.3 (1F, dd, J_{F-F}=285.4 Hz, J_{H-F}=55.5 Hz), −66.6 (1F, dd, J_{F-F}=285.4 Hz, J_{H-F}=55.5 Hz); MS (ESI-TOF) *m*/*z* 270 $[M+H]^+$; HRMS calcd for $C_{15}H_{22}F_2NO$ $[M+H]^+$, 270.1669; found, 270.1668.

4.3. Mono-dechlorination reaction of trichloroacetaldehyde *N*,*O*-acetal

*4.3.1. 3-Allyl-2-(dichloromethyl)-2,3-dihydrobenzo[d]oxazole (**4a**).* To a solution of trichloroacetaldehyde *N*,*O*-acetal **3a** (138.2 mg, 0.5 mmol) in Et_2O (2.0 mL), *n*-BuLi (1.38 M solution in hexane, 0.40 mL, 0.55 mmol) was added at −78 °C for 15 min. After being stirred for 1 h at the same temperature, the mixture was poured into ice water and Et_2O, which was extracted with Et_2O (20 mL×3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. The obtained residue was purified by short column chromatography on silica gel (hexane/EtOAc=25:1) to give dichloroacetaldehyde *N*,*O*-acetal **4a** in 91% yield (111.1 mg, 0.46 mmol). Colorless oil; IR (neat) ν 3063, 2983, 2874, 1487, 1353, 1245, 1208, 1180, 929, 809, 788, 738 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.89 (1H, dd, *J*=15.9, 6.7 Hz), 3.98 (1H, dd, *J*=15.9, 5.1 Hz), 5.28 (1H, dd, *J*=10.2, 1.3 Hz), 5.36 (1H, dd, *J*=17.2, 1.3 Hz), 5.62 (1H, d, *J*=4.2 Hz), 5.72 (1H, d, *J*=4.2 Hz), 5.81–5.95 (1H, m), 6.71 (1H, d, *J*=7.4 Hz), 6.77–6.83 (2H, m), 6.83–6.90 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 72.6, 99.7, 107.9, 110.1, 118.9, 121.0, 121.9, 132.9, 138.8, 150.2; MS (EI) *m*/*z* 243 $[M]^+$, 245 $[M+2]^+$, 247 $[M+4]^+$. Anal. Calcd for $C_{11}H_{11}Cl_2NO$: C, 54.12; H, 4.54; N, 5.74. Found: C, 54.36; H, 4.71; N, 5.58.

4.4. Three component synthesis of α,α-difluoro-β-hydroxyketone *N*,*O*-acetal

*4.4.1. 2-(3-Allyl-2-butyl-2,3-dihydrobenzo[d]oxazol-2-yl)-2,2-difluoro-1-phenylethanol (**5a**).* To a solution of trifluoroacetaldehyde *N*,*O*-acetal **1a** (114.6 mg, 0.5 mmol) in Et_2O (2 mL), *n*-BuLi (1.55 M in hexane, 0.81 mL, 1.25 mmol) was added at −78 °C over 15 min. After being stirred for 4 h at the same temperature, the mixture was treated with a solution of freshly-distilled benzaldehyde (106.9 mg, 1.0 mmol) in Et_2O (1 mL) for 30 min at −78 °C. The resulting mixture was poured into ice water and Et_2O, which was extracted with Et_2O (20 mL×3). The organic phase was washed with brine, dried over anhydrous $MgSO_4$, and evaporated. Purification of the residue by silica gel column chromatography (hexane/EtOAc=20:1) and additional MPLC (hexane/EtOAc=10:1) gave **5a**-*less* (66.3 mg, 0.18 mmol, 36%) and **5a**-*more* (92.4 mg, 0.25 mmol, 49%) in the order of elution. For **5a**-*less* Colorless oil; IR (neat) ν 3543, 3064, 2959, 2872, 1599, 1495, 1401, 1317, 1239, 1031, 731, 731, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J*=7.3 Hz), 1.12–1.26 (1H, m), 1.26–1.52 (3H, m), 2.00–2.13 (1H, m), 2.22–2.35 (1H, m), 2.77 (1H, br s, OH), 3.70–3.82 (2H, m), 5.19–5.26 (2H, m), 5.33 (1H, d, *J*=17.2 Hz), 5.77–5.90 (1H, m), 6.40 (1H, d, 7.6 Hz), 6.62 (1H, t, *J*=7.6 Hz), 6.70 (1H, d, *J*=7.6 Hz), 6.79 (1H, t, *J*=7.6 Hz), 7.29–7.40 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.6, 23.5, 30.5, 47.7 (d, J_{C-F}=2.7 Hz), 72.3 (dd, J_{C-F}=30.5, 22.4 Hz), 104.3 (t, J_{C-F}=29.3 Hz), 105.5, 106.8, 117.1, 118.1, 119.1 (dd, J_{C-F}=265.5, 254.0 Hz), 122.0, 128.05, 128.09, 128.6, 133.9, 136.5, 139.3, 148.6; ^{19}F NMR (282 Hz, $CDCl_3$) δ −60.4 (1F, dd, J_{F-F}=269.6 Hz, J_{H-F}=17.8 Hz), −52.0 (1F, dd, J_{F-F}=269.6 Hz, J_{H-F}=4.0 Hz); MS (ESI-TOF) *m*/*z* 396 $[M+Na]^+$; HRMS calcd for $C_{22}H_{25}F_2NNaO_2$ $[M+Na]^+$, 396.1751; found, 396.1777. Anal. Calcd for $C_{22}H_{25}F_2NO_2$: C, 70.76; H, 6.75; N, 3.75. Found: C, 70.58; H, 6.98; N, 3.58. For **5a**-*more* colorless oil; IR (neat) ν 3540, 3064, 2959, 2872, 1599, 1465, 1316, 1239, 1086, 1062, 929, 732, 699 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J*=7.2 Hz), 1.16–1.52 (4H, m), 2.00–2.18 (2H, m), 3.85 (1H, dd, *J*=16.2, 6.5 Hz), 3.96–4.04 (1H, m), 5.13–5.22 (1H, m), 5.29 (1H, dd, *J*=10.2, 1.3 Hz), 5.40 (1H, dd, *J*=17.2, 1.3 Hz), 5.94–6.07 (1H, m), 6.51 (1H, d, *J*=7.5 Hz), 6.60–6.67 (2H, m), 6.74–6.83 (1H, m), 7.30–7.38 (3H, m), 7.39–7.45 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.6, 23.6, 30.4, 48.1, 72.7 (dd, J_{C-F}=28.7, 23.8 Hz), 103.7 (t, J_{C-F}=29.6 Hz), 105.9, 106.9, 117.6, 118.5, 118.7 (dd, J_{C-F}=260.9, 257.8 Hz), 121.8, 128.0, 128.2, 128.5, 133.9, 136.2, 139.1, 148.8; ^{19}F NMR (282 Hz, $CDCl_3$) δ −63.6 (1F, dd, J_{F-F}=269.3 Hz, J_{H-F}=17.8 Hz), −51.0 (1F, d, J_{F-F}=269.3 Hz); MS (ESI-TOF) *m*/*z* 396 $[M+Na]^+$; HRMS calcd for $C_{22}H_{25}F_2NNaO_2$ $[M+Na]^+$, 396.1751; found, 396.1726. Anal. Calcd for $C_{22}H_{25}F_2NO_2$: C, 70.76; H, 6.75; N, 3.75. Found: C, 70.75; H, 6.77; N, 3.66.

*4.4.2. 2-(3-Allyl-2-butyl-2,3-dihydrobenzo[d]oxazol-2-yl)-2,2-difluoro-1-(4-methoxyphenyl)ethanol (**5b**).* This compound was obtained in 79% yield (*less* 63.8 mg, 0.16 mmol; *more* 95.6 mg, 0.24 mmol) by the reaction of trifluoroacetaldehyde *N*,*O*-acetal **1a** (115.2 mg, 0.5 mmol), *n*-BuLi (1.42 M in hexane, 0.88 mL, 1.25 mmol), and *p*-anisaldehyde (136.4 mg, 1.0 mmol) in Et_2O (3 mL) for 30 min at −78 °C. For **5b**-*less* colorless oil; IR (neat) ν 3469, 3064, 2958, 2871, 1613, 1599, 1514, 1496, 1249, 1069, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, d, *J*=7.3 Hz), 1.12–1.26 (1H, m), 1.26–1.51 (3H, m), 2.00–2.11 (1H, m), 2.22–2.34 (1H, m), 2.69 (1H, br s, OH), 3.74 (1H, dd, *J*=16.4, 6.1 Hz), 3.76–3.84 (1H, m), 3.80 (3H, s), 5.19 (1H, dd, J_{H-F}=17.8, 4.2 Hz), 5.24 (1H, d, *J*=10.3 Hz), 5.33 (1H, d, *J*=17.2 Hz), 5.78–5.90 (1H, m), 6.39 (1H, m), 6.58–6.64 (1H, m), 6.69 (1H, d, *J*=7.6 Hz), 6.75–6.80 (1H, m), 6.86 (2H, d, *J*=8.6 Hz), 7.28 (2H, d, *J*=8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.6, 23.5, 30.5, 47.6 (d, J_{C-F}=2.5 Hz), 55.2, 71.9 (dd, J_{C-F}=30.6, 22.7 Hz), 104.2 (t, J_{C-F}=29.5 Hz), 105.4, 106.8, 113.5, 117.1, 118.0, 119.2 (dd, J_{C-F}=265.6, 253.5 Hz), 122.0, 128.7, 129.3, 133.9, 139.3, 148.6, 159.8; ^{19}F NMR (282 Hz, $CDCl_3$) δ −60.7 (1F, dd, J_{F-F}=269.3 Hz, J_{H-F}=17.8 Hz), −51.3 (1F, dd, J_{F-F}=269.5 Hz, J_{H-F}=4.2 Hz); MS (ESI-TOF) *m*/*z* 426 $[M+Na]^+$; HRMS calcd for $C_{23}H_{27}F_2NNaO_3$ $[M+Na]^+$, 426.1857; found, 426.1863. For **5b**-*more* colorless oil; IR (neat) ν 3485, 3064, 2959, 2872, 1613, 1599, 1514, 1496, 1248, 1176, 1070, 1034, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, d, *J*=7.2 Hz), 1.14–1.50 (4H, m), 1.99–2.16 (2H, m), 3.21 (1H, br s, OH), 3.80 (3H, s), 3.83 (1H, dd, *J*=16.3, 6.2 Hz), 3.96–4.03 (1H, m), 5.09–5.16 (1H, m), 5.27 (1H, dd, *J*=10.2, 1.4 Hz), 5.39 (1H, dd, *J*=17.2, 1.4 Hz), 5.92–6.05 (1H, m), 6.47 (1H, d, *J*=7.5 Hz), 6.59–6.64 (2H, m), 6.73–6.80 (1H, m), 6.86 (2H, d, *J*=8.6 Hz), 7.32 (2H, d, *J*=8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.6, 23.6, 30.4, 48.1, 55.2, 72.3 (dd, J_{C-F}=29.3, 23.2 Hz), 103.7 (t, J_{C-F}=28.6 Hz), 105.9, 106.9, 113.5, 117.6, 118.5, 118.8 (dd, J_{C-F}=260.6, 257.5 Hz), 121.8, 128.3 (d, J_{C-F}=1.2 Hz), 129.4, 133.9, 139.1, 148.8, 159.8; ^{19}F NMR (282 Hz, $CDCl_3$) δ −63.7 (1F, dd, J_{F-F}=267.3 Hz, J_{H-F}=17.8 Hz), −51.3 (1F, d, J_{F-F}=267.3 Hz); MS (ESI-TOF) *m*/*z* 426 $[M+Na]^+$; HRMS calcd for $C_{23}H_{27}F_2NNaO_3$ $[M+Na]^+$, 426.1857; found, 426.1836.

*4.4.3. 2-(3-Allyl-2-butyl-2,3-dihydrobenzo[d]oxazol-2-yl)-2,2-difluoro-1-(4-(trifluoromethyl)phenyl)ethanol (**5c**).* This compound was obtained in 85% yield (*less* 69.5 mg 0.16 mmol; *more* 118.2 mg, 0.27 mmol) by the reaction of trifluoroacetaldehyde *N*,*O*-acetal **1a** (115.2 mg, 0.5 mmol), *n*-BuLi (1.42 M in hexane, 0.88 mL, 1.25 mmol) and 4-trifluoromethylbenzaldehyde (174.1 mg, 1.0 mmol) in Et_2O (3 mL) for 30 min at −78 °C. For **5c**-*less* colorless oil; IR (neat) ν 3485, 3067, 2961, 2874, 1599, 1496, 1326, 1239, 1167, 1127, 1068, 1018, 930, 782, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J*=7.2 Hz), 1.12–1.25 (1H, m), 1.26–1.50 (3H, m), 2.01–2.14 (1H, m), 2.19–2.31 (1H, m), 2.95 (1H, br, OH), 3.70–3.86 (2H, m), 5.21–5.34 (2H, m), 5.34 (1H, d, *J*=16.3 Hz), 5.74–5.90 (1H, m), 6.42 (1H, d, *J*=7.5 Hz), 6.60–6.69 (1H, m), 6.42 (1H, d, *J*=7.5 Hz), 6.60–6.69 (1H, m), 6.70 (1H, d, *J*=7.5 Hz), 6.77–6.84 (1H, m), 7.47 (2H, d, *J*=8.2 Hz), 7.59 (2H, d, *J*=8.2 Hz); ^{13}C NMR (100 MHz, $CDCl_3$)

δ 13.9, 22.6, 23.4, 30.4, 47.9 (d, J_{C-F}=3.0 Hz), 71.9 (dd, J_{C-F}=29.5, 23.3 Hz), 104.4 (t, J_{C-F}=29.4 Hz), 105.8, 107.0, 117.3, 118.5, 118.8 (dd, J_{C-F}=266.2, 254.3 Hz), 122.3, 124.1 (q, J_{C-F}=272.0 Hz), 124.9 (q, J_{C-F}=3.7 Hz), 128.5, 130.7 (q, J_{C-F}=32.5 Hz), 133.7, 139.2, 140.2, 148.4; ^{19}F NMR (282 Hz, $CDCl_3$) δ −59.7 (1F, dd, J_{F-F}=269.6, J_{H-F}=18.0 Hz), −52.3 (1F, d, J_{F-F}=269.6 Hz), 0.05 (3F, s); MS (ESI-TOF) *m*/*z* 464 $[M+Na]^+$; HRMS calcd for $C_{23}H_{24}F_5NNaO_2$ $[M+Na]^+$, 464.1625; found, 464.1628. For **5c**-*more* colorless oil; IR (neat) ν 3500, 3067, 2961, 2874, 1599, 1494, 1326, 1239, 1166, 1127, 1067, 1019, 735 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (3H, t, *J*=7.2 Hz), 1.21–1.52 (4H, m), 2.04–2.20 (2H, m), 3.54 (1H, br s, OH), 3.84 (1H, dd, *J*=16.1, 6.6 Hz), 3.96–4.04 (1H, m), 5.19–5.28 (1H, m), 5.30 (1H, dd, *J*=10.2, 1.4 Hz), 5.42 (1H, dd, *J*=17.2, 1.4 Hz), 5.94–6.07 (1H, m), 6.53 (1H, d, *J*=7.6 Hz), 6.57–6.68 (2H, m), 6.76–6.84 (1H, m), 7.52 (2H, d, *J*=8.3 Hz), 7.58 (2H, d, *J*=8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.8, 22.6, 23.5, 30.3, 48.4, 72.3 (dd, J_{C-F}=28.9, 23.7 Hz), 103.7 (t, J_{C-F}=28.7 Hz), 106.3, 107.1, 117.9, 118.3 (t, J_{C-F}=260.3 Hz), 119.0, 122.0, 124.1 (q, J_{C-F}=272.2 Hz), 124.8 (q, J_{C-F}=3.6 Hz), 128.6, 130.5 (q, J_{C-F}=32.4 Hz), 133.7, 139.0, 140.0, 148.6; ^{19}F NMR (282 Hz, $CDCl_3$) δ −63.4 (1F, dd, J_{F-F}=269.7, 17.9 Hz), −50.8 (1F, d, J_{F-F}=269.7 Hz), 0.05 (3F, s); MS (ESI-TOF) *m*/*z* 442 $[M+H]^+$; HRMS calcd for $C_{23}H_{25}F_5NO_2$ $[M+H]^+$, 442.1805; found, 442.1800.

*4.4.4. 2-(3-Allyl-2-butyl-2,3-dihydrobenzo[d]oxazol-2-yl)-2,2-difluoro-1-(furan-2-yl)ethanol (**5d**).* This compound was obtained in 87% yield (*less* 71.9 mg, 0.198 mmol; *more* 86.3 mg, 0.237 mmol) by the reaction of trifluoroacetaldehyde *N*,*O*-acetal **1a** (115.3 mg, 0.50 mmol), *n*-BuLi (1.42 M in hexane, 0.88 mL, 1.25 mmol), and furfural (96.1 mg, 1.0 mmol) in Et_2O (3 mL) for 1 h at −78 °C. For **5d**-*less* colorless oil; IR (neat) ν 3442, 3065, 2959, 2872, 1599, 1496, 1239, 1110, 1080, 924, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, d, *J*=7.2 Hz), 1.14–1.52 (4H, m), 2.00–2.12 (1H, m), 2.20–2.31 (1H, m), 2.68 (1H, br s, OH), 3.78 (1H, dd, *J*=16.3, 6.3 Hz), 3.81–3.89 (1H, m), 5.19–5.30 (2H, m), 5.33 (1H, d, *J*=17.2 Hz), 5.79–5.83 (1H, m), 6.28–6.36 (2H, m), 6.38 (1H, d, *J*=7.6 Hz), 6.75 (1H, td, *J*=7.6, 1.0 Hz), 6.65 (1H, d, *J*=7.6, 1.0 Hz), 6.71–6.79 (1H, m), 7.39–7.42 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.6, 23.5, 30.4, 47.6, 66.9 (dd, J_{C-F}=30.6, 24.4 Hz), 103.6 (t, J_{C-F}=28.4 Hz), 105.3, 106.7, 109.3, 110.4, 117.1, 118.0, 119.0 (dd, J_{C-F}=264.6, 256.0 Hz), 121.8, 134.0, 139.2, 142.7, 147.7, 149.7; ^{19}F NMR (282 Hz, $CDCl_3$) δ −59.2 (1F, dd, J_{F-F}=267.3 Hz, J_{H-F}=17.8 Hz), −51.3 (1F, dd, J_{F-F}=267.3 Hz, J_{H-F}=5.9 Hz); MS (ESI-TOF) *m*/*z* 386 $[M+Na]^+$; HRMS calcd for $C_{20}H_{23}F_2NNaO_3$ $[M+Na]^+$, 386.1544; found, 386.1543. For **5d**-*more* colorless oil; IR (neat) ν 3521, 3064, 2959, 2872, 1599, 1496, 1240, 1110, 1083, 1060, 1013, 923, 791, 734 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, t, *J*=7.2 Hz), 1.13–1.25 (1H, m), 1.25–1.49 (3H, m), 1.93–2.03 (1H, m), 2.04–2.15 (1H, m), 2.98 (1H, br s, OH), 3.83 (1H, dd, *J*=16.3, 6.3 Hz), 3.95–4.05 (1H, m), 5.17–5.30 (1H, m), 5.26 (1H, dd, *J*=10.3, 1.5 Hz), 5.38 (1H, dd, *J*=17.2, 1.5 Hz), 5.91–6.04 (1H, m), 6.32 (2H, d, *J*=1.3 Hz), 6.46 (1H, d, *J*=7.2 Hz), 6.55–6.63 (2H, m), 6.71–6.79 (1H, m), 7.40 (1H, t, *J*=1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.5, 23.5, 30.1, 48.0, 66.9 (dd, J_{C-F}=29.0, 24.9 Hz), 103.3 (t, J_{C-F}=28.0 Hz), 105.8, 106.9, 109.6, 110.4, 117.5, 118.4, 118.7 (t, J_{C-F}=260.0 Hz), 121.7, 133.9, 139.1, 142.7, 148.8, 149.4 (d, J_{C-F}=3.0 Hz); ^{19}F NMR (282 Hz, $CDCl_3$) δ −60.7 (1F, dd, J_{F-F}=267.6 Hz, J_{H-F}=15.8 Hz), −51.3 (1F, dd, J_{F-F}=267.6 Hz, J_{H-F}=7.9 Hz); MS (ESI-TOF) *m*/*z* 386 $[M+Na]^+$; HRMS calcd for $C_{20}H_{23}F_2NNaO_3$ $[M+Na]^+$, 386.1544; found, 386.1542.

*4.4.5. 2-(3-Allyl-2-butyl-2,3-dihydrobenzo[d]oxazol-2-yl)-2,2-difluoro-1-(pyridin-2-yl)ethanol (**5e**).* This compound was obtained in 87% yield (*less* 125.8 mg, 0.34 mmol; *more* 37.0 mg, 0.099 mmol) by the reaction of trifluoroacetaldehyde *N*,*O*-acetal **1a** (115.6 mg, 0.5 mmol), *n*-BuLi (1.42 M in hexane, 0.88 mL, 1.25 mmol), and 2-pyridinecarbaldehyde (106.9 mg, 1.0 mmol) in Et_2O (3 mL) for 15 min at −78 °C. For **5e**-*less* colorless oil; IR (neat) ν 3365, 3063, 2958, 2871, 1597, 1496, 1402, 1315, 1239, 1206, 1110, 1085, 935, 754, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J*=7.2 Hz), 1.20–1.60 (4H, m), 2.06–2.18 (1H, m), 2.53–2.66 (1H, m), 3.86 (1H, dd, *J*=16.5, 6.0 Hz), 3.94 (1H, dd, *J*=16.5, 5.6 Hz), 5.06–5.60 (1H, br s, OH), 5.20 (1H, dd, *J*=10.4, 1.2 Hz), 5.25 (1H, J_{H-F}=21.7 Hz), 5.34 (1H, dd, *J*=17.2, 1.2 Hz), 5.84–5.97 (1H, m), 6.49 (1H, d, *J*=7.5 Hz), 6.57 (1H, t, *J*=7.5 Hz), 6.65 (1H, d, *J*=7.5 Hz), 6.75 (1H, t, *J*=7.5 Hz), 7.24–7.28 (1H, m), 7.34 (1H, dd, *J*=7.8, 2.7 Hz), 7.61–7.69 (1H, m), 8.54 (1H, d, *J*=4.9 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 23.8, 31.2, 47.2, 70.7 (dd, J_{C-F}=32.4, 24.3 Hz), 103.7 (dd, J_{C-F}=29.3, 24.5 Hz), 104.5, 106.4, 116.8, 117.2, 120.1 (dd, J_{C-F}=264.8, 255.4 Hz), 121.4, 123.47, 123.50 (t, J_{C-F}=5.4 Hz), 134.1, 136.4, 139.4, 147.7, 149.2, 153.8; ^{19}F NMR (282 Hz, $CDCl_3$) δ −61.8 (1F, dd, J_{F-F}=263.4 Hz, J_{H-F}=21.7 Hz), −51.0 (1F, d, J_{F-F}=263.4 Hz); MS (ESI-TOF) *m*/*z* 397 $[M+Na]^+$; HRMS calcd for $C_{21}H_{24}F_2N_2NaO_2$ $[M+Na]^+$, 397.1704; found, 397.1714. Anal. Calcd for $C_{21}H_{24}F_2N_2O_2$: C, 67.36; H, 6.46; N, 7.48. Found: C, 67.35; H, 6.53; N, 7.42. For **5e**-*more* colorless oil; IR (neat) ν 3361, 2958, 2871, 1597, 1495, 1401, 1313, 1241, 1207, 1109, 1085, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J*=7.1 Hz), 1.15–1.51 (4H, m), 2.13–2.31 (2H, m), 3.87 (1H, dd, *J*=16.7, 5.7 Hz), 4.03–4.12 (1H, m), 5.10 (1H, dd, J_{H-F}=17.8, 4.6 Hz), 5.24 (1H, dd, *J*=10.3, 1.5 Hz), 5.39 (1H, dd, *J*=17.2, 1.5 Hz), 5.91–6.02 (1H, m), 6.41 (1H, d, *J*=7.5 Hz), 6.47 (1H, d, *J*=7.6 Hz), 6.51–6.57 (1H, m), 6.70–6.77 (1H, m), 7.26–7.31 (1H, m), 7.34 (1H, d, *J*=8.0 Hz), 7.63–7.70 (1H, m), 8.58 (1H, d, *J*=4.7 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 22.6, 23.7, 31.0, 47.6, 70.9 (dd, J_{C-F}=29.8, 26.2 Hz), 103.6 (t, J_{C-F}=26.5 Hz), 105.3, 106.3, 116.8, 117.7, 119.5 (dd, J_{C-F}=263.0, 257.9 Hz), 121.4, 123.3 (br), 123.5, 134.2, 136.6, 139.6, 147.7, 149.1, 153.9; ^{19}F NMR (282 Hz, $CDCl_3$) δ −60.6 (1F, dd, J_{F-F}=265.6 Hz, J_{H-F}=17.8 Hz), −51.6 (1F, dd, J_{F-F}=265.6 Hz, J_{H-F}=4.6 Hz); MS (ESI-TOF) *m*/*z* 397 $[M+Na]^+$; HRMS calcd for $C_{21}H_{24}F_2N_2NaO_2$ $[M+Na]^+$, 397.1704; found, 397.1678. Anal. Calcd for $C_{21}H_{24}F_2N_2O_2$: C, 67.36; H, 6.46; N, 7.48. Found: C, 67.41; H, 6.66; N, 7.43.

*4.4.6. (E)-1-(3-Allyl-2-butyl-2,3-dihydrobenzo[d]oxazol-2-yl)-1,1-difluoro-4-phenylbut-3-en-2-ol (**5f**).* This compound was obtained in 87% yield (*less* 86.5 mg, 0.236 mmol; *more* 72.1 mg, 0.199 mmol) by the reaction of trifluoroacetaldehyde *N*,*O*-acetal **1a** (115.5 mg, 0.50 mmol), *n*-BuLi (1.42 M in hexane, 0.88 mL, 1.25 mmol), and cinnamaldehyde (132.2 mg, 1.0 mmol) in Et_2O (3 mL) for 1 h at −78 °C. For **5f**-*less* colorless oil; IR (neat) ν 3417, 3061, 2959, 2871, 1599, 1496, 1238, 1070, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (3H, t, *J*=7.2 Hz), 1.17–1.55 (4H, m), 2.05–2.17 (1H, m), 2.22–2.34 (1H, m), 2.52 (1H, br s, OH), 3.82 (1H, dd, *J*=16.3, 6.3 Hz), 3.94 (1H, dd, *J*=16.3, 5.1 Hz), 4.80 (1H, ddd, J_{H-F}=13.8, 9.9 Hz, J_{H-H}=6.9 Hz), 5.22 (1H, d, *J*=10.2 Hz), 5.34 (1H, d, *J*=17.2 Hz), 5.86–5.99 (1H, m), 6.28 (1H, dd, *J*=15.9, 6.9 Hz), 6.37 (1H, d, *J*=7.5 Hz), 6.52 (1H, d, *J*=15.9 Hz), 6.60 (1H, t, *J*=7.5 Hz), 6.68 (1H, d, *J*=7.5 Hz), 6.74 (1H, t, *J*=7.5 Hz), 7.22–7.37 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.5, 23.4, 30.4, 47.8, 71.6 (t, J_{C-F}=26.4 Hz), 103.5 (t, J_{C-F}=29.0 Hz), 105.4, 106.7, 117.2, 118.0, 119.8 (dd, J_{C-F}=261.8, 257.1 Hz), 122.4, 123.5 (t, J_{C-F}=3.2 Hz), 126.7, 127.9, 128.4, 133.7, 133.9, 136.1, 139.2, 148.7; ^{19}F NMR (282 Hz, $CDCl_3$) δ −57.6 (1F, dd, J_{F-F}=267.6 Hz, J_{H-F}=13.8 Hz), −56.4 (1F, dd, J_{F-F}=267.6 Hz, J_{H-F}=9.9 Hz); MS (ESI-TOF) *m*/*z* 422 $[M+Na]^+$; HRMS calcd for $C_{24}H_{27}F_2NNaO_2$ $[M+Na]^+$, 422.1908; found, 422.1899. Anal. Calcd for $C_{24}H_{27}F_2NO_2$: C, 72.16; H, 6.81; N, 3.51. Found: C, 71.91; H, 6.83; N, 3.49. For **5f**-*more* colorless oil; IR (neat) ν 3426, 3061, 2959, 2872, 1599, 1495, 1239, 1069, 733 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, *J*=7.2 Hz), 1.12–1.51 (4H, m), 2.05–2.21 (2H, m), 2.69 (1H, br s, OH), 3.82 (1H, dd, *J*=16.2, 6.4 Hz), 3.98 (1H, dd, *J*=16.2, 4.9 Hz), 4.75 (1H, ddd, J_{H-F}=23.8, 9.2 Hz, J_{H-H}=7.0 Hz), 5.25 (1H, d, *J*=10.2 Hz), 5.36 (1H, d, *J*=17.1 Hz), 5.90–6.03 (1H, m), 6.26 (1H, dd, *J*=16.0, 7.0 Hz), 6.45 (1H, d, *J*=7.6 Hz), 6.50–6.58 (3H, m), 6.69–6.78 (1H, m), 7.20–7.33 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.6, 23.4, 30.2, 48.1, 71.8 (dd, J_{C-F}=27.9, 24.5 Hz), 103.4 (t, J_{C-F}=28.6 Hz), 105.6, 107.3, 117.5,

118.4, 119.4 (t, J_{C-F}=259.1 Hz), 121.7, 123.4 (t, J_{C-F}=3.3 Hz), 126.7, 127.9, 128.4, 133.9, 134.1, 136.2, 139.1, 148.7; ^{19}F NMR (282 Hz, $CDCl_3$) δ −60.8 (1F, dd, J_{F-F}=266.4 Hz, J_{H-F}=12.8 Hz), −54.9 (1F, dd, J_{F-F}=266.4 Hz, J_{H-F}=9.2 Hz); MS (ESI-TOF) *m*/*z* 422 $[M+Na]^+$; HRMS calcd for $C_{24}H_{27}F_2NNaO_2$ $[M+Na]^+$, 422.1908; found, 422.1883. Anal. Calcd for $C_{24}H_{27}F_2NO_2$: C, 72.16; H, 6.81; N, 3.51. Found: C, 71.91; H, 6.91; N, 3.32.

4.4.7. (R)-1-((R*)-3-Allyl-2-butyl-2,3-dihydrobenzo[d]oxazol-2-yl)-1,1-difluoro-4-phenylbutan-2-ol (anti-**5g**).* This compound was obtained in 76% yield (152.6 mg, 0.38 mmol) as an inseparable *anti*/*syn* mixture in a ratio of 11:1 by the reaction of trifluoroacetaldehyde *N*,*O*-acetal **1a** (114.9 mg, 0.5 mmol), *n*-BuLi (1.42 M in hexane, 0.88 mL, 1.25 mmol), and 3-phenylpropionaldehyde (137.1 mg, 1.0 mmol) in Et_2O (3.0 mL) for 3 h at −24 °C. Spectra date only for *anti* isomer (major isomer) are shown. Colorless oil; IR (neat) ν 3547, 3063, 3027, 2959, 2871, 1599, 1495, 1240, 1085, 734, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, t, *J*=7.2 Hz), 1.19–1.33 (1H, m), 1.34–1.59 (3H, m), 1.93–2.06 (1H, m), 2.06–2.20 (3H, m), 2.67–2.78 (2H, m), 2.89–3.00 (1H, m), 3.85 (1H, dd, *J*=16.3, 6.3 Hz), 3.96–4.04 (1H, m), 4.08–4.21 (1H, m), 5.28 (1H, d, *J*=10.2 Hz), 5.37 (1H, d, *J*=17.2 Hz), 5.89–6.01 (1H, m), 6.51 (1H, d, *J*=7.5 Hz), 6.67–6.76 (2H, m), 6.81–6.87 (1H, m), 7.18–7.28 (3H, m), 7.29–7.36 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.6, 23.6, 30.3, 31.4, 48.1, 69.4 (dd, J_{C-F}=29.0, 23.7 Hz), 103.6 (t, J_{C-F}=28.9 Hz), 105.9, 106.8, 117.4, 118.5, 119.5 (t, J_{C-F}=258.6 Hz), 121.8, 125.8, 128.3, 128.4, 133.8, 139.0, 141.4, 148.8; ^{19}F NMR (282 Hz, $CDCl_3$) δ −64.0 (1F, dd, J_{F-F}=267.3 Hz, J_{H-F}=17.8 Hz), −54.6 (1F, d, J_{F-F}=267.3 Hz); MS (ESI-TOF) *m*/*z* 424 $[M+Na]^+$; HRMS calcd for $C_{24}H_{29}F_2NNaO_2$ $[M+Na]^+$, 424.2064; found, 424.2044.

4.4.8. (R)-2-((R*)-3-Allyl-2-butyl-2,3-dihydrobenzo[d]oxazol-2-yl)-1-cyclohexyl-2,2-difluoroethanol (anti-**5h**).* This compound was obtained in 81% yield (153.7 mg, 0.40 mmol) as an inseparable *anti*/*syn* mixture in a ratio of 11:1 by the reaction of trifluoroacetaldehyde *N*,*O*-acetal **1a** (115.4 mg, 0.5 mmol), *n*-BuLi (1.42 M in hexane, 0.88 mL, 1.25 mmol), and cyclohexanecarbaldehyde (112.3 mg, 1.0 mmol) in Et_2O (3.0 mL) for 8 h at 0 °C. Spectra date only for *anti* isomer (major isomer) are shown. Colorless crystals; mp 49.0–50.0 °C; IR (neat) ν 3564, 2929, 2854, 1599, 1496, 1240, 1089, 924, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.90 (3H, t, *J*=7.2), 1.08–1.52 (9H, m), 1.53–1.61 (1H, m), 1.62–1.70 (1H, m), 1.70–1.94 (4H, m), 2.11 (2H, t, *J*=7.4 Hz), 2.51 (1H, br s, OH), 3.81 (1H, dd, *J*=16.3, 6.3 Hz), 3.86–4.06 (2H, m), 5.27 (1H, dd, *J*=10.3, 1.4 Hz), 5.38 (1H, dd, *J*=17.1, 1.4 Hz), 5.91–6.04 (1H, m), 6.47 (1H, d, *J*=7.5 Hz), 6.59–6.70 (2H, m), 6.73–6.80 (1H, td, *J*=7.5, 1.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ for major isomer 13.9, 22.6, 23.7, 26.1, 26.2 (2C), 26.7, 30.2, 30.4, 38.4 (d, J_{C-F}=2.5 Hz), 48.2, 73.1 (dd, J_{C-F}=28.2, 22.2 Hz), 103.8 (t, J_{C-F}=28.9 Hz), 105.8, 106.7, 117.4, 118.4, 120.2 (t, J_{C-F}=260.4 Hz), 121.7, 134.0, 139.3, 149.0; ^{19}F NMR (282 Hz, $CDCl_3$) δ −60.6 (1F, dd, J_{F-F}=269.6 Hz, J_{H-F}=21.7 Hz), −52.6 (1F, d, J_{F-F}=269.6 Hz); MS (ESI-TOF) *m*/*z* 402 $[M+Na]^+$; HRMS calcd for $C_{22}H_{31}F_2NNaO_2$ $[M+Na]^+$, 402.2221; found, 402.2206. Anal. Calcd for $C_{22}H_{31}F_2NO_2$: C, 69.63; H, 8.23; N, 3.69. Found: C, 69.82; H, 8.11; N, 3.73.

*4.4.9. 1-(3-Allyl-2-butyl-2,3-dihydrobenzo[d]oxazol-2-yl)-1,1-difluoro-2-methylpropan-2-ol (**5i**).* This compound was obtained in 89% yield (144.8 mg, 0.45 mmol) by the reaction of trifluoroacetaldehyde *N*,*O*-acetal **1a** (115.7 mg, 0.5 mmol), *n*-BuLi (1.42 M in hexane, 0.88 mL, 1.25 mmol), and acetone (58.2 mg, 1.0 mmol) in Et_2O (3 mL) for 9 h at room temperature. Colorless oil; IR (neat) ν 3464, 3064, 2959, 2873, 1599, 1496, 1239, 1071, 732 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, t, *J*=7.3 Hz), 1.11–1.25 (1H, m), 1.26–1.50 (3H, m), 1.36 (3H, s), 1.40 (3H, s), 2.03–2.16 (1H, m), 2.22–2.36 (1H, m), 2.59 (1H, br s, OH), 3.82 (1H, dd, *J*=16.1, 6.5 Hz), 3.99 (1H, dd, *J*=16.1, 4.9 Hz), 5.26 (1H, d, *J*=10.3 Hz), 5.38 (1H, d, *J*=17.2 Hz), 5.91–6.06 (1H, m), 6.47 (1H, d, *J*=7.4 Hz), 6.58–6.67 (2H, m), 6.73–6.80 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.6, 23.7, 14.7 (t, J_{C-F}=3.2 Hz), 25.6 (t, J=3.3 Hz), 31.9, 48.4, 74.2 (t, J_{C-F}=26.4 Hz), 104.8 (dd, J_{C-F}=30.4, 29.6 Hz), 105.7, 106.7, 117.4, 118.3, 120.7 (t, J_{C-F}=260.9 Hz), 121.7, 134.0, 139.1, 148.8; ^{19}F NMR (282 Hz, $CDCl_3$) δ −55.9 (1F, d, *J*=271.4 Hz), −53.6 (1F, d, *J*=271.4 Hz); MS (ESI-TOF) *m*/*z* 326 $[M+H]^+$; HRMS calcd for $C_{18}H_{26}F_2NO_2$ $[M+H]^+$, 326.1964; found, 326.1964.

*4.4.10. 1-((3-Allyl-2-butyl-2,3-dihydrobenzo[d]oxazol-2-yl)difluoromethyl)cyclohexanol (**5j**).* This compound was obtained in 84% yield (153.5 mg, 0.42 mmol) by the reaction of trifluoroacetaldehyde *N*,*O*-acetal **1a** (115.7 mg, 0.5 mmol), *n*-BuLi (1.42 M in hexane, 0.88 mL, 1.25 mmol), and cyclohexanone (97.2 mg, 1.0 mmol) in Et_2O (3 mL) for 5 h at 0 °C. Colorless oil; IR (neat) ν 3548, 3064, 2936, 2864, 1599, 1496, 1239, 1086, 989, 731 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (3H, t, *J*=7.3 Hz), 1.08–1.22 (2H, m), 1.24–1.48 (3H, m), 1.51–1.79 (8H, m), 1.91–2.00 (1H, m), 2.02–2.13 (1H, m), 2.23–2.34 (1H, m), 2.26 (1H, br s, OH), 3.81 (1H, dd, *J*=16.2, 6.5 Hz), 3.94–4.03 (1H, m), 5.25 (1H, dd, *J*=10.2, 1.4 Hz), 5.37 (1H, dd, *J*=17.2, 1.4 Hz), 5.91–6.03 (1H, m), 6.45 (1H, d, *J*=7.5 Hz), 6.57–6.67 (2H, m), 6.75 (1H, td, *J*=7.5, 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.0, 20.8, 20.9, 22.6, 23.8, 25.3, 30.6 (m), 31.5 (t, J_{C-F}=3.3 Hz), 32.2, 48.3, 75.4 (t, J_{C-F}=25.2 Hz), 105.2 (t, J_{C-F}=28.8 Hz), 105.6, 106.6, 117.3, 118.1, 120.7 (t, J_{C-F}=260.9 Hz), 121.6, 134.1, 139.3, 148.9; ^{19}F NMR (282 Hz, $CDCl_3$) δ −57.4 (1F, d, J_{F-F}=271.6 Hz), −55.8 (1F, d, J_{F-F}=271.6 Hz); MS (ESI-TOF) *m*/*z* 388 $[M+Na]^+$; HRMS calcd for $C_{21}H_{29}F_2NNaO_2$ $[M+Na]^+$, 388.2064; found, 388.2071. Anal. Calcd for $C_{21}H_{29}F_2NO_2$: C, 69.02; H, 8.00; N, 3.83. Found: C, 68.98; H, 7.91; N, 3.73.

*4.4.11. 1-(3-Allyl-2-butyl-2,3-dihydrobenzo[d]oxazol-2-yl)-1,1-difluoro-2-phenylpropan-2-ol (**5k**).* This compound were obtained in 79% yield (*less* 98.4 mg, 0.254 mmol; *more* 54.6 mg, 0.141 mmol) by the reaction of trifluoroacetaldehyde *N*,*O*-acetal **1a** (115.6 mg, 0.5 mmol), *n*-BuLi (1.42 M in hexane, 0.88 mL, 1.25 mmol), and acetophenone (120.3 mg, 1.0 mmol) in Et_2O (3 mL) for 9 h at room temperature. For **5k**-*less* Colorless oil; IR (neat) ν 3542, 3062, 2959, 2872, 1599, 1496, 1239, 1093, 1067, 925, 732, 700 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.82 (3H, t, *J*=7.2 Hz), 1.04–1.17 (1H, m), 1.18–1.38 (3H, m), 1.76 (3H, s), 1.79–1.89 (1H, m), 1.89–2.00 (1H, m), 3.82 (1H, dd, *J*=16.0, 6.8 Hz), 3.92–4.01 (1H, m), 4.06 (1H, br s, OH), 5.34 (1H, dd, *J*=10.2, 1.4 Hz), 5.44 (1H, dd, *J*=17.2, 1.4 Hz), 5.99–6.01 (1H, m), 6.33 (1H, dd, *J*=7.7, 0.9 Hz), 6.52 (1H, dd, *J*=7.5, 1.1 Hz), 6.55–6.60 (1H, m), 6.75–6.81 (1H, m), 7.24–7.33 (3H, m), 7.46–7.52 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.7, 22.4, 23.4, 25.5 (t, J_{C-F}=3.7 Hz), 31.5, 48.5, 76.7–77.3 (m), 105.0 (t, J_{C-F}=29.9 Hz), 106.0, 106.9, 117.8, 118.7, 119.9 (t, J_{C-F}=264.0 Hz), 121.6, 125.4 (d, J_{C-F}=2.4 Hz), 127.2, 127.6, 133.9, 138.8, 142.1 (d, J_{C-F}=3.4 Hz), 148.3; ^{19}F NMR (282 Hz, $CDCl_3$) δ −53.8 (1F, d, J_{F-F}=271.3 Hz), −48.9 (1F, d, J_{F-F}=271.3 Hz); MS (ESI-TOF) *m*/*z* 410 $[M+Na]^+$; HRMS calcd for $C_{23}H_{27}F_2NNaO_2$ $[M+Na]^+$, 410.1908; found, 410.1872. Anal. Calcd for $C_{23}H_{27}F_2NO_2$: C, 71.30; H, 7.02; N, 3.61. Found: C, 71.32; H, 7.04; N, 3.48. For **5k**-*more* colorless oil; IR (neat) ν 3548, 3062, 2959, 2872, 1599, 1496, 1239, 1090, 1074, 921, 732, 701 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (3H, t, *J*=7.2 Hz), 1.08–1.20 (1H, m), 1.22–1.41 (3H, m), 1.74 (3H, s), 1.93–2.04 (1H, m), 2.15–2.25 (1H, m), 3.23 (1H, br s, OH), 3.62 (1H, dd, *J*=16.2, 5.4 Hz), 3.69 (1H, dd, *J*=16.2, 6.6 Hz), 5.21 (1H, dd, *J*=10.2, 1.4 Hz), 5.30 (1H, dd, *J*=17.2, 1.4 Hz), 5.81–5.94 (1H, m), 6.26 (1H, dd, *J*=7.5, 1.0 Hz), 6.47 (1H, dd, *J*=7.6, 1.0 Hz), 6.54–6.61 (1H, m), 6.68–6.74 (1H, m), 7.23–7.34 (3H, m), 7.42–7.49 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13.9, 22.5, 23.5, 26.4 (t, J_{C-F}=3.5 Hz), 31.7, 47.7, 76.5–77.1 (m), 104.8 (t, J_{C-F}=29.8 Hz), 105.7, 106.7, 117.4, 118.0, 120.2 (t, J_{C-F}=263.8 Hz), 121.5, 126.1, 127.2, 127.5, 133.9, 138.6, 141.4 (d, J_{C-F}=2.8 Hz), 148.6; ^{19}F NMR (282 Hz, $CDCl_3$) δ −52.4 (1F, d,

J_{F-F}=271.3 Hz), −50.2 (1F, d, J_{F-F}=271.3 Hz); MS (ESI-TOF) *m*/*z* 410 $[M+Na]^+$; HRMS calcd for $C_{23}H_{27}F_2NNaO_2$ $[M+Na]^+$, 410.1908; found, 410.1889.

4.5. Three component synthesis of β-amino-α,α-difluoroketone *N*,*O*-acetal

*4.5.1. 2-(3-Allyl-2-butyl-2,3-dihydrobenzo[d]oxazol-2-yl)-2,2-difluoro-N,N-dimethylethanamine (**6**).* To a solution of trifluoroacetaldehyde *N*,*O*-acetal **1a** (113.9 mg, 0.5 mmol) in Et_2O (2.0 mL), *n*-BuLi (1.45 M solution in hexane, 0.86 mL, 1.25 mmol) was added at −78 °C. After being stirred for 4 h at the same temperature, the resulting mixture was treated with *N*,*N*-dimethylmethyleneiminium chloride (93.9 mg, 1.00 mmol) at room temperature for 24 h. The reaction mixture was poured into ice water (15 mL) and Et_2O (20 mL), which was extracted with Et_2O (20 mL×3). The combined organic layer was washed with brine (10 mL), dried over anhydrous Na_2SO_4, and evaporated. Purification of the residue by column chromatography on silica gel (hexane/EtOAc=5:1) gave β-amino-α,α-difluroketone *N*,*O*-acetal **6** in 77% yield (125.2 mg, 0.39 mmol). Colorless oil; IR (neat) *ν* 3063, 2958, 2871, 2826, 2775, 1599, 1496, 1228, 1073, 923, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 0.88 (3H, t, *J*=7.2 Hz), 1.10–1.22 (1H, m), 1.25–1.49 (3H, m), 2.06 (2H, t, *J*=7.9 Hz), 2.35 (6H, s), 2.85 (1H, td, *J*=14.8, 9.1 Hz), 2.94 (1H, td, *J*=14.8, 8.5 Hz), 3.79 (1H, dd, *J*=16.3, 5.6 Hz), 3.88–3.97 (1H, m), 5.22 (1H, dd, *J*=10.2, 1.4 Hz), 5.34 (1H, dd, *J*=17.2, 1.4 Hz), 5.84–5.96 (1H, m), 6.39 (1H, d, *J*=7.5 Hz), 6.54–6.60 (1H, m), 6.64 (1H, d, *J*=7.6 Hz), 6.70–6.76 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 13.9, 22.6, 23.5, 29.5, 47.2, 47.6, 57.8 (t, J_{C-F}=21.9 Hz), 103.0 (t, J_{C-F}=28.7 Hz), 104.9, 106.5, 117.0, 117.8, 121.5, 122.2 (dd, J_{C-F}=257.1, 252.6 Hz), 133.9, 139.4, 149.1; ^{19}F NMR (282 Hz, $CDCl_3$) *δ* −54.8 to −53.6 (1F, m), −51.4 to −50.3 (1F, m); MS (ESI-TOF) *m*/*z* 325 $[M+H]^+$; HRMS calcd for $C_{18}H_{27}F_2N_2O$ $[M+H]^+$, 325.2091; found, 325.2102. Anal. Calcd for $C_{18}H_{26}F_2N_2O$: C, 66.64; H, 8.08; N, 8.64. Found: C, 66.71; H, 7.99; N, 8.63.

4.6. Three component synthesis of difluorohalomethyl ketone *N*,*O*-acetal

*4.6.1. 3-Allyl-2-butyl-2-(chlorodifluoromethyl)-2,3-dihydrobenzo[d]oxazole (**7a**).* To a solution of trifluoroacetaldehyde *N*,*O*-acetal **1a** (113.9 mg, 0.5 mmol) in Et_2O (2.5 mL), *n*-BuLi (1.48 M solution in hexane, 0.84 mL, 1.25 mmol) was added at −78 °C. After being stirred for 4 h, the resulting mixture was treated with *N*-chlorosuccinimide (134.8 mg, 1.0 mmol) at the same temperature for 7 h. The reaction mixture was quenched with saturated aqueous solution of $Na_2S_2O_3$ (15 mL), and extracted with Et_2O (20 mL×3). The combined organic layer was washed with brine (10 mL), dried over anhydrous $MgSO_4$, and evaporated. Purification of the residue by column chromatography on silica gel (hexane/EtOAc=100:1) gave chlorodifluoromethylketone *N*,*O*-acetal **7a** in 73% yield (109.8 mg, 0.37 mmol). Colorless oil; IR (neat) *ν* 3065, 2961, 2873, 1601, 1495, 1241, 1123, 1046, 911, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 0.92 (3H, t, *J*=7.2 Hz), 1.19–1.58 (4H, m), 2.07–2.25 (2H, m), 3.87 (1H, dd, *J*=16.7, 6.0 Hz), 3.95–4.03 (1H, m), 5.28 (1H, dd, *J*=10.3, 1.2 Hz), 2.39 (1H, dd, *J*=17.3, 1.2 Hz), 5.86–5.98 (1H, m), 6.47 (1H, d, *J*=7.5 Hz), 6.65 (1H, td, *J*=7.5, 1.1 Hz), 6.74 (1H, d, *J*=7.5 Hz), 6.79 (1H, dt, *J*=7.5, 1.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 13.9, 22.5, 23.8, 29.7, 47.5, 103.4 (t, J_{C-F}=26.6 Hz), 105.5, 106.8, 117.2, 118.3, 121.7, 128.9 (dd, J_{C-F}=307.6, 305.5 Hz), 133.4, 138.8, 148.9; ^{19}F NMR (282 Hz, $CDCl_3$) *δ* −5.81 (1F, d, J_{F-F}=167.5 Hz), −4.71 (1F, d, J_{F-F}=167.5 Hz); MS (ESI-TOF) *m*/*z* 302 $[M+H]^+$; HRMS calcd for $C_{15}H_{19}ClF_2NO$ $[M+H]^+$, 302.1123; found, 302.1131.

*4.6.2. 3-Allyl-2-butyl-2-(difluoroiodomethyl)-2,3-dihydrobenzo[d]oxazole (**7b**).* According to the synthetic procedure for **7a**, this compound was obtained in 88% yield (172.6 mg, 0.44 mmol) by the reaction of trifluoroacetaldehyde *N*,*O*-acetal **1a** (114.0 mg, 0.5 mmol), *n*-BuLi (1.48 M solution in hexane, 0.84 mL, 1.25 mmol), and *N*-iodosuccinimide (223.9 mg, 1.00 mmol) at −78 °C for 4 h in Et_2O (2.5 mL). Colorless oil; IR (neat) *ν* 3065, 2959, 2872, 1600, 1494, 1237, 1095, 1031, 771, 732 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 0.90 (3H, t, *J*=7.2 Hz), 1.18–1.57 (4H, m), 2.04–2.14 (1H, m), 2.14–2.25 (1H, m), 3.84 (1H, dd, *J*=16.5, 6.3 Hz), 3.92–4.01 (1H, m), 5.28 (br d, *J*=10.2 Hz), 5.41 (1H, br d, *J*=17.2 Hz), 5.89–6.01 (1H, m), 6.49 (1H, d, *J*=7.6 Hz), 6.61–6.68 (1H, m), 6.74 (1H, d, *J*=7.6 Hz), 6.76–6.82 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 13.9, 22.6, 24.1, 28.9, 47.6, 104.5 (t, J_{C-F}=23.2 Hz), 105.5, 107.0, 108.7 (dd, J_{C-F}=332.1, 326.6 Hz), 117.5, 118.4, 121.8, 133.6, 139.0, 148.8; ^{19}F NMR (282 Hz, $CDCl_3$) *δ* 6.2 (1F, d, J_{F-F}=188.3 Hz), 10.6 (1F, d, J_{F-F}=188.3 Hz); MS (ESI-TOF) *m*/*z* 394 $[M+H]^+$; HRMS calcd for $C_{15}H_{19}F_2INO$ $[M+H]^+$, 394.0479; found, 394.0495.

4.7. Reformatsky type reaction of trichloroacetaldehyde *N*,*O*-acetal

*4.7.1. 2-(3-Allyl-2,3-dihydrobenzo[d]oxazol-2-yl)-2,2-dichloro-1-phenylethanol (**8a**).* To a solution of trichloroacetaldehyde *N*,*O*-acetal **3a** (138.0 mg, 0.5 mmol) in Et_2O (2 mL), *n*-BuLi (1.38 M in hexane, 0.40 mL, 0.55 mmol) was added at −78 °C for 15 min. After being stirred for 1 h at the same temperature, the mixture was treated with a mixture of freshly-distilled benzaldehyde (101 μg, 1.0 mmol) and $BF_3{\cdot}OEt$ (0.3 mL, 3.0 mmol) in Et_2O (1 mL) for 30 min at −78 °C. The resulting mixture was poured into ice water and Et_2O, which was extracted with Et_2O (20 mL×3). The organic phase was washed with brine, dried over $MgSO_4$, and evaporated. Purification of the residue by silica gel column chromatography (hexane/EtOAc=10:1) and additional MPLC (hexane/EtOAc=6:1) gave **8a**-*less* (102.6 mg, 0.29 mmol, 58% yield) and **8a**-*more* (46.6 mg, 0.13 mmol, 27% yield). For **8a**-*less* Pale yellow oil; IR (neat) *ν* 3444, 3064, 3033, 2925, 1487, 1239, 868, 737, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 2.76 (1H, br, OH), 3.94 (1H, dd, *J*=16.0, 7.2 Hz), 4.08–4.16 (1H, m), 5.27 (1H, d, *J*=10.3 Hz), 5.36 (1H, d, *J*=17.2 Hz), 5.43 (1H, s), 5.81–5.95 (1H, m), 6.18 (1H, s), 6.74–6.83 (3H, m), 6.83–6.91 (1H, m), 7.35–7.45 (3H, m), 7.56–7.63 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 56.7, 77.3, 95.8, 99.5, 107.4, 110.4, 118.7, 120.8, 121.8, 127.7, 128.9, 129.0, 133.0, 137.2, 139.7, 151.0; MS (ESI-TOF) *m*/*z* 350 $[M+H]^+$; HRMS calcd for $C_{18}H_{18}Cl_2NO_2$ $[M+H]^+$, 350.0715; found, 350.0730. Anal. Calcd for $C_{18}H_{17}Cl_2NO_2$: C, 61.73; H, 4.89; N, 4.00. Found: C, 61.88; H, 4.75; N, 4.10. For **8a**-*more* colorless crystals; 106.0–107.5 °C; IR(KBr) *ν* 3434, 3062, 3033, 2925, 1488, 1241, 868, 740, 702 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) *δ* 3.11 (1H, br s, OH), 3.82 (1H, dd, *J*=16.1, 7.0 Hz), 3.98–4.05 (1H, m), 5.22 (1H, dd, *J*=10.3, 1.5 Hz), 5.30 (1H, dd, *J*=17.2, 1.5 Hz), 5.36 (1H, s), 5.64 (1H, s), 5.75–5.89 (1H, m), 6.76 (1H, d, *J*=7.2 Hz), 6.79–6.89 (3H, m), 7.36–7.44 (3H, m), 7.58–7.66 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) *δ* 56.3, 77.2, 97.2, 100.4, 107.5, 110.6, 118.6, 121.2, 121.8, 128.0, 128.7, 129.0, 132.9, 136.5, 139.5, 150.9; MS (ESI-TOF) *m*/*z* 350 $[M+H]^+$; HRMS calcd for $C_{18}H_{18}Cl_2NO_2$ $[M+H]^+$, 350.0715; found, 350.0718. Anal. Calcd for $C_{18}H_{17}Cl_2NO_2$: C, 61.73; H, 4.89; N, 4.00. Found: C, 61.60; H, 4.93; N, 4.14.

4.7.2. (R)-2-((R*)-3-Allyl-2,3-dihydrobenzo[d]oxazol-2-yl)-1-(2-bromophenyl)-2,2-dichloroethanol (anti-**8b**) and (S*)-2-((R*)-3-allyl-2,3-dihydrobenzo[d]oxazol-2-yl)-1-(2-bromophenyl)-2,2-dichloroethanol (syn-**8b**).* According to the synthetic procedure for **8a**, these compounds were obtained in 72% (154.7 mg, 0.36 mmol) as an *anti*/*syn* mixture in a ratio of 2.3:1 by the reaction of trichloroacetaldehyde *N*,*O*-acetal **3a** (138.8 mg, 0.5 mmol), *n*-BuLi (1.52 M solution in hexane, 0.36 mL, 0.55 mmol), and 2-bromobenzaldehyde (185.2 mg, 1.0 mmol) in Et_2O (3.0 mL) in the presence of $BF_3{\cdot}OEt_2$ (0.3 mL, 3.0 mmol) at −78 °C for 2 h. The stereochemistry of these products was determined by an X-ray

crystallographic analysis of *syn* isomer. For ***syn*-8b** (less polar isomer) colorless crystals; mp 115.0–118.5 °C; IR (KBr) ν 3419, 3064, 2926, 1487, 1239, 875, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.95 (1H, dd, J=15.9, 7.3 Hz), 4.08–4.16 (1H, m), 5,29 (1H, dd, J=10.3, 1.1 Hz), 5.38 (1H, dd, J=17.2, 1.1 Hz), 5.84–5.97 (1H, m), 6.06 (1H, s), 6.13 (1H, s), 6.77–6.82 (3H, m), 6.82–6.89 (1H, m), 7.23 (1H, td, J=7.8, 1.4 Hz), 7.35–7.43 (1H, m), 7.58 (1H, dd, J=7.8, 1.0 Hz), 7.99 (1H, dd, J=7.8, 1.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.1, 74.0, 95.9, 99.8, 107.5, 110.8, 119.0, 121.2, 121.8, 125.5, 127.1, 130.21, 130.24, 132.8, 132.9, 137.1, 139.5, 150.1; MS (ESI-TOF) m/z 428 $[M+H]^+$; HRMS calcd for $C_{18}H_{17}BrCl_2NO_2$ $[M+H]^+$, 427.9820; found, 427.9835. Anal. Calcd for $C_{18}H_{16}BrCl_2NO_2$: C, 50.38; H, 3.76; N, 3.26. Found: C, 50.10; H, 4.66; N, 3.33. For ***anti*-8b** (more polar isomer) pale yellow oil; IR (neat) ν 3420, 3064, 2926, 1487, 1241, 841, 816, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.64 (1H, br s, OH), 3.93 (1H, dd, J=15.9, 7.4 Hz), 4.10–4.18 (1H, m), 5.32 (1H, dd, J=10.3, 1.2 Hz), 5.41 (1H, dd, J=17.1, 1.2 Hz), 5.84–5.97 (1H, m), 5.87 (1H, s), 5.98 (1H, s), 6.80–6.92 (4H, m), 7.23 (1H, td, J=8.0, 1.6 Hz), 7.35–7.42 (1H, m), 7.58 (1H, dd, J=8.0, 1.1 Hz), 7.92 (1H, dd, J=7.3, 1.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.7, 73.8, 94.7, 102.2, 107.9, 111.4, 119.5, 121.98, 122.01, 125.4, 127.2, 130.27, 130.33, 132.4, 132.7, 136.8, 139.0, 150.8; MS (ESI-TOF) m/z 428 $[M+H]^+$; HRMS calcd for $C_{18}H_{17}BrCl_2NO_2$ $[M+H]^+$, 427.9820; found, 427.9845.

*4.7.3. 2-(3-Allyl-2,3-dihydrobenzo[d]oxazol-2-yl)-1-(4-bromophenyl)-2,2-dichloroethanol (**8c**).* According to the synthetic procedure for **8a**, these compounds were obtained in 80% (171.2 mg, 0.40 mmol) as a mixture of diastereomers in a ratio of 2.3:1 by the reaction of trichloroacetaldehyde *N*,*O*-acetal **3a** (139.5 mg, 0.5 mmol), *n*-BuLi (1.52 M in hexane, 0.36 mL, 0.55 mmol), and 4-bromobenzaldehyde (185.0 mg, 1.0 mmol) in Et_2O (3.0 mL) in the presence of $BF_3\cdot OEt_2$ (0.3 mL, 3.0 mmol) at −78 °C for 1 h. For **8c**-*less* Pale yellow oil; IR (neat) ν 3403, 3068, 2925, 1487, 1072, 1011, 874, 812, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.26 (1H, br s, OH), 3.82 (1H, dd, J=16.1, 7.0 Hz), 3.97–4.07 (1H, m), 5.24 (1H, d, J=10.3 Hz), 5.30 (1H, d, J=17.1 Hz), 5.31 (1H, s), 5.63 (1H, s), 5.75–5.90 (1H, m), 6.76 (1H, d, J=7.1 Hz), 6.79–6.91 (3H, m), 7.48 (2H, d, J=8.4 Hz), 7.52 (2H, d, J=8.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.4, 76.6, 96.7, 100.5, 107.6, 110.7, 118.8, 121.3, 122.0, 123.2, 130.5, 131.1, 132.7, 135.5, 139.3, 150.8; MS (ESI-TOF) m/z 428 $[M+H]^+$; HRMS calcd for $C_{18}H_{17}BrCl_2NO_2$ $[M+H]^+$, 427.9820; found, 427.9835. Anal. Calcd for $C_{18}H_{16}BrCl_2NO_2$: C, 50.38; H, 3.76; N, 3.26. Found: C, 50.26; H, 3.80; N, 3.15. For **8c**-*more* Pale yellow oil; IR (neat) ν 3404, 3063, 2924, 1487,1240, 1073, 1011, 810, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.82 (1H, dd, J=16.1, 7.0 Hz), 3.97–4.05 (1H, m), 5.24 (1H, dd, J=10.2, 1.0 Hz), 5.31 (1H, dd, J=17.0, 1.0 Hz), 5.32 (1H, s), 5.62 (1H, s), 5.75–5.82 (1H, m), 6.76 (1H, d, J=7.3 Hz), 6.79–6.90 (3H, m), 7.48 (2H, d, J=8.6 Hz), 7.52 (2H, d, J=8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.7, 76.6, 95.3, 99.5, 107.4, 110.6, 118.8, 120.9, 121.9, 123.1, 130.7, 130.9, 132.9, 136.2, 139.6, 150.9; MS (ESI-TOF) m/z 428 $[M+H]^+$; HRMS calcd for $C_{18}H_{17}BrCl_2NO_2$ $[M+H]^+$, 427.9820; found, 427.9840.

*4.7.4. (E)-1-(3-Allyl-2,3-dihydrobenzo[d]oxazol-2-yl)-1,1-dichloro-4-phenylbut-3-en-2-ol (**8d**).* According to the synthetic procedure for **8a**, these compounds were obtained in 75% (140.5 mg, 0.37 mmol) as an inseparable mixture of diastereomers in a ratio of 1.4:1 (*less*/*more*) by the reaction of trichloroacetaldehyde *N*,*O*-acetal **3a** (139.3 mg, 0.5 mmol), *n*-BuLi (1.52 M solution in hexane, 0.36 mL, 0.55 mmol), and cinnamaldehyde (132.3 mg, 1.0 mmol) in Et_2O (3.0 mL) in the presence of $BF_3\cdot OEt_2$ (0.3 mL, 3.0 mmol) at −78 °C for 2 h. Pale yellow oil; IR (neat) ν 3403, 3060, 3025, 2926, 1488, 1241, 968, 860, 824, 744, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ for a mixture of diastereomers 3.92 (0.58H, dd, J=16.1, 7.2 Hz) and 3.88 (0.42H, dd, J=16.5, 7.0 Hz), 4.05–4.15 (1H, m), 4.98 (0.58H, dd, J=6.1, 1.1 Hz) and 4.89 (0.42H, dd, J=6.1, 1.1 Hz), 5.26 (1H, br d, J=10.3 Hz), 5.36 (1H, br d, J=17.2 Hz), 5.80–5.94 (1H, m), 6.09 (0.58H, s) and 5.97 (0.42H, s), 6.54 (0.58H, dd, J=15.9, 6.1 Hz) and 6.45 (0.42H, dd, J=15.9, 6.6 Hz), 6.72–6.89 (5H, m), 7.25–7.30 (3H, m), 7.41–7.48 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ for major isomer 56.6, 76.2, 96.4, 99.1, 107.4, 110.5, 118.7, 120.8, 121.8, 124.9, 126.9, 128.3, 128.7, 133.0, 135.2, 136.0, 139.7, 151.0, for minor isomer 55.9, 76.2, 96.8, 100.5, 107.6, 110.6, 118.8, 121.3, 121.7, 124.5, 126.9, 128.4, 128.7, 132.8, 135.6, 135.9, 139.5, 151.1; MS (ESI-TOF) m/z 376 $[M+H]^+$; HRMS calcd for $C_{20}H_{20}Cl_2NO_2$ $[M+H]^+$, 376.0871; found, 376.0886.

*4.7.5. 2-(3-Benzyl-2,3-dihydrobenzo[d]oxazol-2-yl)-1-(4-bromophenyl)-2,2-dichloroethanol (**8e**).* According to the synthetic procedure for **8a**, these compounds were obtained in 80% (171.2 mg, 0.40 mmol) as a mixture of diastereomers in a ratio of 2.3:1 by the reaction of trichloroacetaldehyde *N*,*O*-acetal **3b** (164.5 mg, 0.5 mmol), *n*-BuLi (1.52 M solution in hexane, 0.36 mL, 0.55 mmol), and 4-bromobenzaldehyde (185.3 mg, 1.0 mmol) in Et_2O (3.0 mL) in the presence of $BF_3\cdot OEt_2$ (0.3 mL, 3.0 mmol) at −78 °C for 1 h. For **8e**-*less* colorless oil; IR (neat) ν 3420, 3064, 3029, 2928, 2871, 1488, 1362, 1257, 1011, 808, 737 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.08 (1H, br s, OH), 4.38 (1H, d, J=15.5 Hz), 4,60 (1H, d, J=15.5 Hz), 5.29 (1H, s), 5.63 (1H, s), 6.50–6.56 (1H, m), 6.78–6.83 (3H, m), 7.27–7.37 (5H, m), 7.44 (2H, d, J=8.6 Hz), 7.51 (2H, d, J=8.6 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.2, 76.8, 97.1, 100.6, 107.7, 110.7, 121.3, 122.0, 123.3, 127.6, 127.7, 128.7, 130.4, 131.2, 135.4, 137.1, 139.9, 150.7; MS (ESI-TOF) m/z 478 $[M+H]^+$; HRMS calcd for $C_{22}H_{19}BrCl_2NO_2$ $[M+H]^+$, 477.9976; found, 477.9957. For **8e**-*more* Brown amorphous solid; mp 40.5–49.0 °C; IR (neat) ν 3496, 3064, 3029, 2925, 1488, 1258, 1073, 1011, 876, 813, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.80 (1H, br s, OH), 4.50 (1H, d, J=15.6 Hz), 4.73 (1H, d, J=15.6 Hz), 5.40 (1H, s), 6.19 (1H, s), 6.48–6.53 (1H, m), 6.76–6.82 (3H, m), 7.27–7.39 (5H, m), 7.44 (2H, d, J=8.5 Hz), 7.52 (2H, d, J=8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.0, 76.7, 95.5, 99.8, 107.4, 110.3, 120.7, 121.9, 123.1, 127.6, 127.7, 128.7, 130.7, 130.9, 136.1, 137.4, 140.1, 150.7; MS (ESI-TOF) m/z 478 $[M+H]^+$; HRMS calcd for $C_{22}H_{19}BrCl_2NO_2$ $[M+H]^+$, 477.9976; found, 477.9964.

*4.7.6. 1-(4-Bromophenyl)-2,2-dichloro-2-(3-propyl-2,3-dihydrobenzo[d]oxazol-2-yl)ethanol (**8f**).* According to the synthetic procedure for **8a**, these compounds were obtained in 72% (154.4 mg, 0.36 mmol) as an inseparable mixture of diastereomers in a ratio of 2.0:1 by the reaction of trichloroacetaldehyde *N*,*O*-acetal **3c** (140.4 mg, 0.5 mmol), *n*-BuLi (1.52 M solution in hexane, 0.36 mL, 0.55 mmol), and 4-bromobenzaldehyde (185.0 mg, 1.0 mmol) in Et_2O (3.0 mL) in the presence of $BF_3\cdot OEt_2$ (0.3 mL, 3.0 mmol) at −78 °C for 1 h. Pale yellow oil; IR (neat) ν 3413, 3060, 2964, 2874, 1488, 1243, 1074, 1011, 812, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ for a mixture of diastereomers 0.93 (1.98H, t, J=7.4 Hz) and 0.90 (1.02H, t, J=7.4 Hz), 1.57–1.80 (2H, m), 3.18–3.42 (2H, m), 5.39 (0.66H, s) and 5.32 (0.34H, s), 6.12 (0.66H, s) and 5.56 (0.34H, s), 6.70–6.75 (1H, m), 6.75–6.82 (2H, m), 6.83–6.90 (1H, m), 7.42–7.56 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ for major isomer 11.4, 20.5, 55.6, 76.7, 95.2, 100.3, 107.3, 110.2, 120.4, 121.9, 123.1, 130.7, 130.9, 136.2, 139.8, 150.8, for minor isomer 11.3, 20.5, 55.6, 76.7, 96.7, 101.1, 107.6, 110.5, 121.0, 122.0, 123.2, 130.5, 131.2, 135.5, 139.3, 150.7; MS (ESI-TOF) m/z 430 $[M+H]^+$; HRMS calcd for $C_{18}H_{19}BrCl_2NO_2$ $[M+H]^+$, 429.9976; found, 429.9959.

4.7.7. (S)-1-((R*)-3-Allyl-2,3-dihydrobenzo[d]oxazol-2-yl)-1,1,3,3,3-pentachloropropan-2-ol (anti-**8g**) and (R*)-1-((R*)-3-allyl-2,3-dihydrobenzo[d]oxazol-2-yl)-1,1,3,3,3-pentachloropropan-2-ol (syn-**8g**).* According to the synthetic procedure for **8a**, these compounds were obtained in 65% (127.8 mg, 0.33 mmol) as an *anti*/*syn* mixture in

a ratio of 1.4:1 by the reaction of trichloroacetaldehyde *N*,*O*-acetal **3a** (139.5 mg, 0.5 mmol), *n*-BuLi (1.52 M solution in hexane, 0.36 mL, 0.55 mmol), and chloral (147.5 mg, 1.0 mmol) in Et_2O (3.0 mL) at room temperature for 5 h. The stereochemistry of these products was determined by an X-ray crystallographic analysis of *syn* isomer. For ***syn*-8g** (less polar isomer) colorless crystals; mp 111.0–113.0 °C; IR (KBr) ν 3502, 3068, 2930, 1488, 1239, 866, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.66 (1H, br s, OH), 3.93 (1H, dd, J=16.2, 7.1 Hz), 4.06–4.17 (1H, m), 4.98 (1H, br s), 5.27(1H, d, J=10.2 Hz), 5.38 (1H, d, J=17.1 Hz), 5.81–5.89 (1H, m), 6.12 (1H, s), 6.73–6.82 (3H, m), 6.82–6.88 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 57.0, 83.0, 91.4, 99.8, 100.6, 107.4, 110.4, 118.7, 120.9, 122.0, 132.9, 139.8, 150.7; MS (ESI-TOF) m/z 390 $[M+H]^+$; HRMS calcd for $C_{13}H_{13}Cl_5NO_2$ $[M+H]^+$, 389.9389; found, 389.9401. For ***anti*-8g** (more polar isomer) colorless oil; IR (neat) ν 3423, 3064, 2985, 2933, 1488, 1306, 1236, 1140, 738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.72 (1H, br s, OH), 3.88 (1H, dd, J=16.1, 7.0 Hz), 4.04–4.13 (1H, m), 4.84 (1H, s), 5.30 (1H, dd, J=10.3, 1.3 Hz), 5.48 (1H, dd, J=17.2, 1.3 Hz), 5.79–5.91 (1H, m), 6.15 (1H, s), 6.75–6.90 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.8, 82.0, 93.2, 99.1, 101.2, 107.7, 111.0, 119.0, 121.8, 121.9, 132.7, 139.6, 151.2; MS (ESI-TOF) m/z 389 $[M+H]^+$; HRMS calcd for $C_{13}H_{13}Cl_5NO_2$ $[M+H]^+$, 389.9389; found, 389.9409.

*4.7.8. Ethyl 3-(3-allyl-2,3-dihydrobenzo[d]oxazol-2-yl)-3,3-dichloro-2-hydroxy-2-(trifluoromethyl)propanoate (**8h**).* According to the synthetic procedure for **8a**, these compounds were obtained in 51% (105.8 mg, 0.26 mmol) as an inseparable mixture of diastereomers in a ratio of 2.3:1 by the reaction of trichloroacetaldehyde *N*,*O*-acetal **3a** (139.4 mg, 0.5 mmol), *n*-BuLi (1.52 M solution in hexane, 0.36 mL, 0.55 mmol), and chloral (147.5 mg, 1.0 mmol) in Et_2O (3.0 mL) at room temperature for 24 h. Colorless oil; IR (neat) ν 3429, 3068, 2985, 2942, 1743, 1488, 1306, 1237, 1177, 1141, 739 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ for a mixture of diastereomers 1.39 (1.97H, t, J=7.1 Hz) and 1.40 (1.03H, t, J=7.2 Hz), 3.81 (0.66H, dd, J=15.8, 7.6 Hz) and 3.92 (0.34H, dd, J=15.6, 7.4 Hz), 3.96–4.04 (0.66H, m) and 4.08–4.16 (0.34H, m), 4.47 (1.31H, q, J=7.1 Hz) and 4.42–4.57 (0.69H, m), 4.87 (0.66H, s) and 4.97 (0.34H, s), 5.25 (1H, br d, J=10.2 Hz), 5.30 (0.66H, br d, J=17.1 Hz) and 5.34 (0.34H, br d, J=17.1 Hz), 5.73–5.88 (1H, m), 6.05 (0.66H, s) and 6.07 (0.34H, s), 6.72–6.89 (3.66H, m) and 6.58 (0.34H, d, J=7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ for major isomer 13.8, 57.3, 65.1, 81.3 (q, J_{C-F}=30.2 Hz), 91.6, 98.5, 107.7, 111.4, 119.4, 121.7, 121.8, 121.9 (q, J_{C-F}=287.9 Hz), 132.4, 139.2, 151.4, 166.3, for minor isomer 13.8, 57.1, 65.4, 79.9 (q, J_{C-F}=29.6 Hz), 90.3, 98.3, 107.1, 110.9, 119.0, 121.0, 122.16, 122.20 (q, J_{C-F}=289.4 Hz), 132.6, 139.5, 150.7, 166.7; MS (ESI-TOF) m/z 414 $[M+H]^+$; HRMS calcd for $C_{16}H_{17}Cl_2F_3NO_4$ $[M+H]^+$, 414.0487; found, 414.0495.

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Supplementary data

Compound characterization data, ^1H and ^{13}C NMR spectra. Supplementary data associated with this article can be found in online version at doi:10.1016/j.tet.2010.04.061.

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