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Stereoselective oxidation of 4-aryl-1,4-dihydropyridines to axially chiral 4-arylpyridines with 2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate ($TEMPO^+BF_4^-$)

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Abstract—Enantiopure 4-aryl-1,4-dihydropyridines (DHPs) were oxidised with 2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate **1** to axially chiral 4-arylpyridines with excellent yields and high enantiomeric excesses. The results can be rationalised via a hydride abstraction of **1** at C-(4) of the DHP from the less sterically shielded *ap*-conformer.

1. Introduction

4-Aryl-1,4-dihydropyridines (DHPs) are important cardiovascular drugs due to their calcium antagonistic effect.[1] The pharmacological activity of chiral DHPs as calcium antagonists or calcium agonists depends on the configuration of the stereogenic centre at C-(4).[1] Enantiopure DHPs are prepared preferentially by resolution of the racemates,[1] which limits the yield to 50% and produces up to 50% of the unwanted enantiomer. In order to overcome this disadvantage a method was developed to interconvert one DHP enantiomer into the other by stereoselective oxidation of enantiopure 4-aryl-1,4-dihydropyridines to axially chiral 4-arylpyridines.[2] These are subsequently reduced back to DHPs with an overall inversion of configuration. 4-Arylpyridines find use in the treatment of arteriosclerosis.[3] They are frequently prepared by oxidation of 1,4-dihydropyridines. Oxidation of nonracemic 4-aryl-DHPs with $NOBF_4$ leads to atropisomeric 4-arylpyridines with inversion of configuration† (Scheme 1).[2] Because of some disadvantages of $NOBF_4$ (lability, moisture sensitivity) and in order to explore the stereoselectivity of oxidants with a related structure, we investigated the oxidation of enantiopure 4-aryl-1,4-dihydropyridines with 2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate ($TEMPO^+BF_4^-$) **1**.[4,5]

2. Results and discussion

The results of the oxidation of **2a–d** with **1** are summarised in Table 1. For comparison **2a–d** were oxidised additionally with nitrosonium tetrafluoroborate.

As can be seen **2a–d** are oxidised by **1** to the corresponding 4-arylpyridines in high yield and with e.e.'s of over 90%. Oxidation with **1** differs from $NOBF_4$ oxidation in that the enantioselectivity remains highly independent from the substitution pattern of **2** and additionally, instead of inversion, retention of configuration is seen. With MnO_2 as the oxidant high stereoselectivity with retention of configuration is seen,[2] however, with a small substituent R^1 at the 4-phenyl group ($R^1 = CH_3$, **2d**) the e.e. decreases to 68%.

In order to explain the selectivity, some knowledge of the oxidation mechanism of DHPs by **1** is necessary. Oxidation can occur by an outer electron transfer, by hydride or radical abstraction or addition of **1** followed by elimination of the corresponding hydroxylamine. An electron transfer between **1** and **2** leading to TEMPO and **3** appears unlikely because the difference between the reduction potential of **1** ($E_{p,red} = 0.74$ V vs. Ag/AgCl) and the oxidation potential of **2** ($E_{p,ox}$ [**2a**] = 1.26 V) is too negative for a reasonably fast electron transfer; and TEMPO, which would be the product of the electron transfer, cannot oxidise **2**. In the oxidation of **2**, only one equivalent of **1** is necessary, the stoichiometry also excludes an electron transfer. Hydride or hydrogen abstraction can occur at the benzylic C-(4) or

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† For this reaction the term inversion is used if an (*S*)-DHP is oxidised to an axial chiral (*R*)-pyridine and retention if an (*S*)-DHP is converted into an (*S*)-pyridine.

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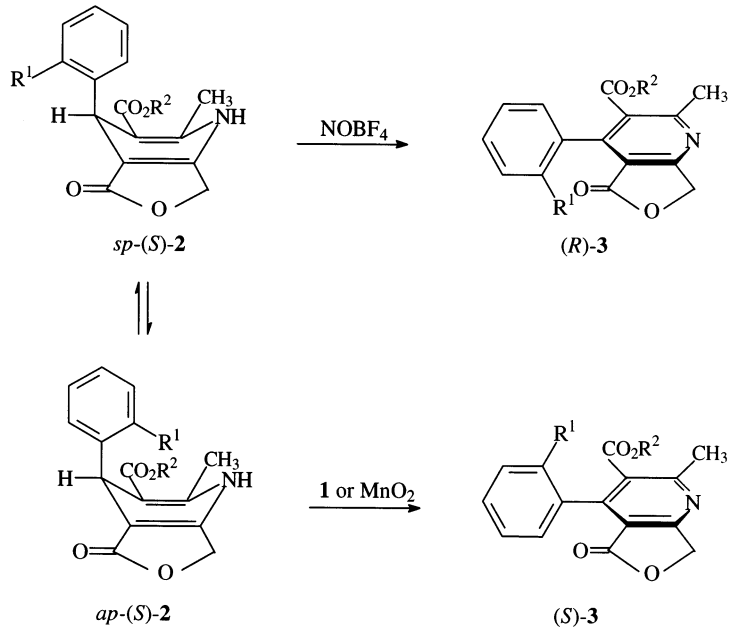


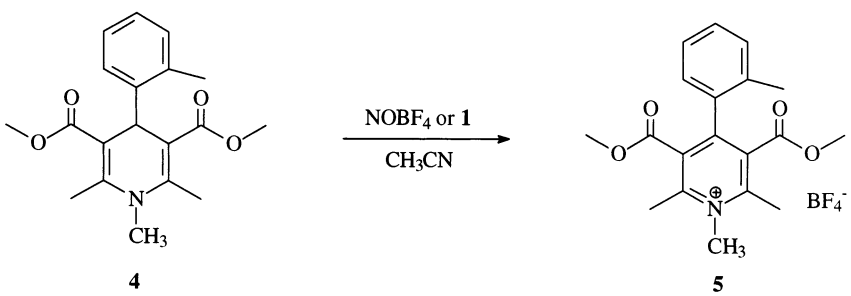
Scheme 1.‡

Table 1. Oxidation of enantiopure 1,4-dihydropyridines **2a–d** to axially chiral 4-aryl-substituted pyridines **3a–d** with 2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate **1** and $NOBF_4$

Entry	Substrate	R^1	R^2	**3**: Oxidation with $NOBF_4$		**3**: Oxidation with **1**	
				Yield (%)	E.e. (%)	Yield (%)	E.e. (%)
1	(*S*)-**2a**	SEt	Et	82	95 (*R*)	94	93 (*S*)
2	(*S*)-**2b**	CH_2Bn	Et	91	49 (*R*)	94	96 (*S*)
3	(*S*)-**2c**	^{n}Prop	Et	88	44 (*R*)	90	93 (*S*)
4	(*R*)-**2d**	Me	^{i}Prop	91	56 (*S*)	91	97 (*R*)

at N as proposed by Olah[6] and Snader,[7] respectively. The first case is, however, more reasonable than the second one, because the intermediate benzylic cation or radical is more stable than the nitrenium cation or nitrogen radical. Furthermore the *N*-methyl-DHP **4**[8] can be oxidised with **1** or $NOBF_4$ to the pyridinium salt **5** in 83 or 79% yield, respectively (Scheme 2). This also makes hydride or hydrogen abstraction at N less reasonable.

An addition of $NOBF_4$ at C-(3) of the double bond of **2**, as it occurs in the addition of *N*-iodosuccinimide to DHP,[9] and subsequent elimination of the hydroxylamine corresponding to **1** cannot be excluded. However, **1** appears too bulky for that route. Also the addition of the C–(4)H bond of **2** to **1**, as it is the case for the oxidation of alcohols with **1**,[10] appears unlikely, because of the low acidity of this proton. Thus the key step in the oxidation will most likely be the hydride



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Scheme 2.

‡ In the case of **2d** and **3d** the configuration is opposite to **2a–c** and **3a–c** because of the CIP rules.

abstraction at C-(4) by **1** or NO^+, followed by deprotonation to give **3**. The ratio of enantiomers will be determined by steric interactions in the hydride abstraction step and will thus depend on the conformation of **2**.

X-Ray structure analyses show that DHPs **2** assume preferentially a boat conformation with the phenyl ring in a pseudoaxial position and substituents R^1 oriented *syn*-periplanar (*sp*) (Scheme 1).[11] PM3 calculations of **2a** or **c** show a preference for the *sp*- over the *ap*-conformer with 3.5 or 3.6 kcal/mol and a rotational barrier of 13.9 or 12.0 kcal/mol, respectively. Thus the bulky $TEMPO^+$ should react preferably with the *ap*-conformer, where the benzylic hydrogen is sterically less shielded by the R^1-substituent leading this way from (*S*)-**2** to (*S*)-**3** with retention of configuration. The less bulky NO^+ reacts with the *sp*-conformer leading to (*R*)-**3** with inversion of configuration (Scheme 1).

In summary, enantiopure 4-aryl-1,4-dihydropyridines **2** can be oxidised with 2,2,6,6-tetramethyl-1-oxopiperidinium tetrafluoroborate **1** in high yield and high enantiomeric excess to atropisomeric 4-arylpyridines. The results can be rationalised via a hydride abstraction of **1** at C-(4) of **2** from the sterically less shielded *ap*-conformer.

3. Experimental

3.1. General

Flash chromatography was performed on Merck silica gel 60 (40–63 μm). Chiral HPLC was performed with a Knauer pump 64.00, a Knauer spectrophotometer 287.00, a Shimadzu integrator C-R3A and a Grom column (250 mm length, 2 mm i.d., stationary phase: Chira OJ mod, mobile phase: *n*-heptane/ethanol 9:1 (0.1% H_2O, 0.02% trifluoroacetic acid)). IR spectra were recorded on a Bruker IFS 28 FT-IR spectrometer. NMR spectra were obtained from a Bruker WM 300 spectrometer (^1H: 300 MHz, ^{13}C: 75.4 MHz). ESI mass spectra were recorded on a Micromass quadrupole mass spectrometer Quattro LC-Z. Optical rotations were measured with a Perkin–Elmer 241 polarimeter. Microanalyses were performed by the analytical laboratory of the Institut für Organische Chemie, Universität Münster. Nitrosonium tetrafluoroborate and 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) were purchased from Aldrich.

3.2. Preparation of enantiopure 2

To obtain the enantiopure DHPs **2** the racemic free carboxylic acids were separated by preparative chiral HPLC.[12] Afterwards the pure enantiomers were esterified in DMF with the alkyl iodide and caesium fluoride.

The configuration of **2e** ($R^1 = SCH_2CH_2Ph$, $R^2 = H$, Scheme 1) was determined by X-ray analysis.[2] The configurations of **2a–d** were inferred from **2e** by comparing the optical rotations, the biological activity, and the elution sequence in chiral HPLC.

(*S*)-**2a**: mp 219–221°C; $[\alpha]_D^{20} = -73.1$ ($c = 0.75$, DMSO); IR (KBr): 3269, 3091, 2965, 2921, 1732, 1691, 1659, 1603, 1504, 1468, 1388, 1254, 1203, 1148, 1089, 761 cm^{-1}; ^1H NMR ($CDCl_3$): δ 1.06 (t, 3H, $J = 7.2$ Hz), 1.28 (t, 3H, $J = 7.4$ Hz), 2.36 (s, 3H), 3.04 (m, 2H), 3.97 (q, 2H, $J = 7.4$ Hz), 4.68 (s, 2H), 5.54 (s, 1H), 7.05–7.38 (m, 4H), 7.62 (s, 1H); ^{13}C NMR ($CDCl_3$): δ 13.5 (q), 13.8 (q), 18.7 (q), 29.1 (t), 35.6 (d), 58.9 (t), 64.5 (t), 103.4 (s), 106.5 (s), 125.9 (d), 126.2 (d), 129.8 (d), 130.3 (d), 135.1 (s), 143.6 (s), 145.4 (s), 154.8 (s), 167.1 (s), 168.5 (s). Anal. calcd for $C_{19}H_{21}NO_4S$: C, 63.49; H, 5.89; N, 3.90. Found: C, 63.04, H, 5.91; N, 3.65%.

(*S*)-**2b**: mp 90–92°C; $[\alpha]_D^{20} = -72.5$ ($c = 0.91$, MeOH); IR (KBr): 3267, 3024, 2970, 2930, 1730, 1695, 1673, 1508, 1452, 1386, 1252, 1195, 1095, 1030, 753, 700 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.95 (t, 3H, $J = 6.8$ Hz), 2.31 (s, 3H), 2.92–3.31 (m, 4H), 3.91 (q, 2H, $J = 7.0$ Hz), 4.77, 4.83 (2d, 2H, $J = 16.2$ Hz), 5.04 (s, 1H), 7.03–7.31 (m, 9H), 9.73 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 14.1 (q), 19.0 (q), 32.8 (d), 34.0 (t), 36.1 (t), 59.3 (t), 65.2 (t), 101.7 (s), 104.4 (s), 125.8 (d), 126.2 (d), 126.5 (d), 128.3 (d), 128.4 (d), 129.2 (d), 138.5 (s), 142.6 (s), 145.0 (s), 156.3 (s), 162.8 (s), 166.9 (s), 171.2 (s). Anal. calcd for $C_{25}H_{25}NO_4$: C, 74.42; H, 6.25; N, 3.47. Found: C, 74.19; H, 6.16; N, 3.33%.

(*S*)-**2c**: mp 218–220°C; $[\alpha]_D^{20} = -131.9$ ($c = 0.91$, DMSO); IR (KBr): 3263, 3098, 3010, 2961, 2929, 1734, 1696, 1667, 1605, 1504, 1446, 1381, 1255, 1195, 1149, 1092, 1022, 763, 719 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.98 (2t, 6H), 1.72 (m, 2H), 2.31 (s, 3H), 2.89 (t, 2H, $J = 8.1$ Hz), 3.88 (q, 2H, $J = 7.2$ Hz), 4.73, 4.80 (2d, 2H, $J = 15.8$ Hz), 4.97 (s, 1H), 7.04–7.10 (m, 4H), 9.67 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 13.8 (q), 14.4 (q), 18.8 (q), 22.7 (t), 32.7 (d), 33.7 (t), 59.0 (t), 64.9 (t), 101.5 (s), 104.2 (s), 125.9 (d), 127.9 (d), 128.9 (d), 139.9 (s), 144.6 (s), 144.8 (s), 155.9 (s), 166.7 (s), 171.3 (s). Anal. calcd for $C_{20}H_{23}NO_4$: C, 70.36; H, 6.79; N, 4.10. Found: C, 70.44; H, 6.96; N, 3.99%.

(*R*)-**2d**: mp 191–193°C; $[\alpha]_D^{20} = -133.9$ ($c = 0.75$, MeOH); IR (KBr): 3267, 3022, 2971, 2942, 1739, 1699, 1661, 1611, 1512, 1445, 1376, 1259, 1201, 1089, 1019, 766, 719 cm^{-1}; ^1H NMR (DMSO-d_6): δ 0.91 (d, 3H, $J = 6.2$ Hz), 1.28 (d, 3H, $J = 6.2$ Hz), 2.52 (s, 3H), 2.73 (s, 3H), 4.89 (qq, 1H, $J = 6.2$ Hz), 4.93, 5.01 (2d, 2H, $J = 12.6$ Hz), 5.09 (s, 1H), 7.16–7.46 (m, 4H), 9.81 (s, 1H); ^{13}C NMR (DMSO-d_6): δ 18.8 (q), 19.4 (q), 20.9 (q), 21.7 (q), 33.1 (d), 65.2 (t), 69.1 (d), 101.7 (s), 104.2 (s), 125.9 (d), 126.2 (d), 128.6 (d), 129.3 (d), 134.9 (s), 145.4 (s), 145.6 (s), 155.8 (s), 166.2 (s), 171.7 (s). Anal. calcd for $C_{19}H_{21}NO_4$: C, 69.71; H, 6.47; N, 4.28. Found: C, 69.51; H, 6.55; N, 4.12%.

3.3. Oxidation of 2 with 1 and $NOBF_4$

In a typical experiment under an argon atmosphere at room temperature a solution of the oxidising agent (1.1

equiv.) in abs. acetonitrile (5 mL) was added dropwise to a stirred solution of **2** (0.25 mmol) in abs. acetonitrile (20 mL). After 1 h the solvent was removed under reduced pressure, and saturated aqueous sodium hydrogencarbonate solution (20 mL) was added to the residue and the aqueous phase was extracted twice with toluene/ethyl acetate (1:1 v/v). The combined organic phase was then concentrated under reduced pressure and the crude product was purified by column chromatography (SiO_2, elution with diethyl ether/cyclohexane 3:1). The configuration of enantiopure **3e** ($R^1=SCH_2CH_2Ph$, $R^2=Et$, Scheme 1) was determined by X-ray analysis.[2] Those of **3a**–**d** were inferred from **3e** by comparing the optical rotations and the elution sequence in chiral HPLC.

(*S*)-**3a**: Mp: 98–100°C; $[\alpha]_D^{20}=+118.6$ ($c=1.2$, MeOH); e.e.=93%; (HPLC); IR (KBr): 2978, 2930, 1782, 1713, 1597, 1575, 1454, 1279, 1188, 1145, 1031, 746 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.94 (t, 3H, $J=7.2$ Hz), 1.20 (t, 3H, $J=7.4$ Hz), 2.76 (s, 3H), 2.85 (m, 2H), 4.05 (m, 2H), 5.22, 5.32 (2d, 2H, $J=16.2$ Hz), 7.07–7.45 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 13.5 (q), 14.1 (q), 23.7 (q), 28.2 (t), 61.6 (t), 69.4 (t), 115.7 (s), 125.8 (d), 128.4 (d), 129.5 (d), 129.7 (d), 130.4 (s), 133.8 (s), 135.7 (s), 147.1 (s), 163.0 (s), 166.5 (s), 166.6 (s), 167.1 (s). Anal. calcd for $C_{19}H_{19}NO_4S$: C, 63.85; H, 5.36; N, 3.92. Found: C, 63.61; H, 5.29; N, 4.01%.

(*S*)-**3b**: Mp 69–70°C; $[\alpha]_D^{20}=+17.8$ ($c=1.0$, MeOH); e.e.=96%; (HPLC); IR (KBr): 3061, 3025, 2980, 2936, 2873, 1776, 1728, 1591, 1573, 1494, 1452, 1274, 1248, 1185, 1145, 1033, 756, 700 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.92 (t, 3H, $J=7.2$ Hz), 2.58–2.83 (m, 4H), 2.74 (s, 3H), 4.03 (q, 2H, $J=7.2$ Hz), 5.22, 5.28 (2d, 2H, $J=16.2$ Hz), 7.00–7.41 (m, 9H); ^{13}C NMR ($CDCl_3$): δ 13.5 (q), 23.6 (q), 35.0 (t), 36.1 (t), 61.7 (t), 69.4 (t), 115.4 (s), 125.7 (d), 125.9 (d), 128.5 (d), 129.3 (d), 130.9 (s), 131.7 (s), 139.5 (s), 141.5 (s), 148.0 (s), 162.8 (s), 166.6 (s), 166.7 (s), 167.2 (s); HRMS (ESI): 424.1535 (calcd for $C_{25}H_{23}NNaO_4$ 424.1525).

(*S*)-**3c**: Mp 52–53°C; $[\alpha]_D^{20}=+63.4$ ($c=0.9$, MeOH); e.e.=93%; (HPLC); IR (KBr): 3061, 2967, 2934, 2873, 1767, 1723, 1592, 1570, 1493, 1452, 1381, 1274, 1249, 1185, 1147, 1035, 745, 658 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.81 (t, 3H, $J=7.4$ Hz), 0.91 (t, 3H, $J=7.1$ Hz), 1.51 (m, 2H), 2.39 (m, 2H), 2.75 (s, 3H), 4.01 (q, 2H, $J=7.1$ Hz), 5.23, 5.33 (2d, 2H, $J=16.2$ Hz), 7.00–7.19 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 13.5 (q), 14.0 (q), 23.0 (t), 23.7 (q), 35.1 (t), 61.7 (t), 69.4 (t), 115.5 (s), 125.3 (s), 128.1 (s), 128.6 (s), 129.2 (d), 130.9 (s), 131.8 (s), 140.3 (s), 148.3 (s), 162.8 (s), 166.7 (s), 166.8 (s), 167.2 (s). Anal. calcd for $C_{20}H_{21}NO_4$: C, 70.78; H, 6.24; N, 4.13. Found: C, 70.77; H, 6.41; N, 3.95%.

(*R*)-**3d**: Mp 138–140°C; $[\alpha]_D^{20}=+99.3$ ($c=1.1$, MeOH); e.e.=97%; (HPLC); IR (KBr): 3068, 2983, 2961, 1775, 1719, 1591, 1573, 1496, 1457, 1384, 1278, 1186, 1148, 1104, 1027, 913, 771, 755 cm^{-1}; ^1H NMR ($CDCl_3$): δ 0.84 (d, 3H, $J=6.3$ Hz), 1.04 (d, 3H, $J=6.3$ Hz), 2.10 (s, 3H), 2.74 (s, 3H), 4.91 (qq, 1H, $J=6.3$ Hz), 5.23, 5.31 (2d, 2H, $J=16.2$ Hz), 7.01–7.39 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 19.6 (q), 20.7 (q), 21.3 (q), 23.5 (q), 69.4 (t), 69.6 (d), 115.3 (s), 125.4 (d), 127.8 (d), 129.2 (d), 129.7 (d), 131.0 (s), 132.2 (s), 135.1 (s), 148.0 (s), 162.6 (s), 166.3 (s), 166.6 (s), 167.2 (s). Anal. calcd for $C_{19}H_{19}NO_4$: C, 70.14; H, 5.89: N, 4.30. Found: C, 69.98; H, 5.90; N, 4.49%.

3.4. Preparation of 4

Compound **4** was prepared following the procedure by Karrer[8] in 22% yield after recrystallisation from methanol as a light yellow solid.

Compound **4**: mp 153–155°C; IR (KBr): 3343, 3015, 2951, 1693, 1644, 1584, 1478, 1388, 1354, 1212, 1161, 1106, 1005, 931, 754, 728 cm^{-1}; ^1H NMR ($CDCl_3$): δ 2.44 (s, 6H), 2.48 (s, 3H), 3.25 (s, 3H), 3.65 (s, 6H), 5.24 (s, 1H), 6.99–7.10 (m, 4H); ^{13}C NMR ($CDCl_3$): δ 16.7 (q), 19.3 (q), 35.2 (d), 43.1 (q), 50.9 (q), 107.6 (s), 126.1 (d), 126.4 (d), 128.0 (d), 130.2 (d), 135.2 (s), 145.9 (s), 148.4 (s), 168.5 (s). Anal. calcd for $C_{19}H_{23}NO_4$: C, 69.28; H, 7.04; N, 4.25. Found: C, 68.94; H, 7.00; N, 4.07%.

3.5. Oxidation of 4 with 1 and $NOBF_4$

Compound **4** was oxidised as described for **2**. For work-up the solvent was removed under reduced pressure and the residue taken up in diethyl ether. The precipitate from the chilled ethereal solution was collected, washed with cold diethyl ether and then with tetrahydrofuran and afterwards vacuum dried. Compound **5** was obtained as a white solid.

Compound **5**: mp 209–212°C; IR (KBr): 3041, 2956, 1738, 1615, 1562, 1441, 1250, 1155, 1061, 761, 725 cm^{-1}; ^1H NMR (acetone-d_6): δ 2.14 (s, 3H), 2.89 (s, 6H), 3.59 (s, 6H), 4.28 (s, 3H), 7.05–7.44 (m, 4H); ^{13}C NMR (acetone-d_6): δ 18.5 (q), 19.0 (q), 40.9 (q), 52.5 (q), 124.5 (d), 127.1 (d), 129.7 (d), 133.1 (d), 133.3 (s), 135.2 (s), 152.8 (s), 154.2 (s), 163.6 (s). Anal. calcd for $C_{19}H_{22}BF_4NO_4$: C, 54.96; H, 5.34; N, 3.37. Found: C, 54.64; H, 5.14; N, 3.18%.

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