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Preparative Scale Synthesis of the Biaryl Core of Anacetrapib via a Ruthenium-Catalyzed Direct Arylation Reaction: Unexpected Effect of Solvent Impurity on the Arylation Reaction†

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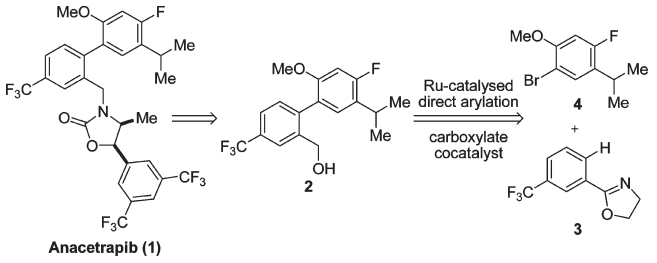

In this report, we disclose our findings regarding the remarkable effect of a low-level impurity found in the solvent used for a ruthenium-catalyzed direct arylation reaction. This discovery allowed for the development of a robust and high-yield arylation protocol that was demonstrated on a multikilogram scale using carboxylate as the cocatalyst. Finally, a practical, scalable, and chromatography-free synthesis of the biaryl core of Anacetrapib is described.

Transition metal catalysis has contributed significantly to the synthesis of biaryl molecules. The most common methods involve the use of palladium catalysts and require activation of both coupling partners.[1] Recently, direct arylation has emerged as an increasingly viable alternative to traditional cross-coupling reactions.[2] In these transformations, the organometallic cross-coupling partner is substituted with a simple arene (Ar-H), thus minimizing the number of functional group manipulations prior to cross-coupling. Importantly, this strategy not only is advantageous because of its economical and ecological benefits but also allows for streamlining organic syntheses. In this context, the use of direct arylation represents an interesting option for the large scale preparation of active pharmaceutical ingredients such as Anacetrapib (**1**), a compound currently in development at Merck for the treatment of hypercholesterolemia.

Atherosclerosis is the leading cause of illness and death in North America, Europe, and most developed countries.[3] It is believed that an increase in HDL level ("good cholesterol") could result in a decrease in the incidence of arteriosclerotic vascular disease. One promising new approach targets cholesteryl ester transfer protein (CETP). This glycoprotein is involved in the recycling of HDL particles into less desirable LDL and VLDL.[4]

Anacetrapib (MK-0859, **1**)[5] has been identified as a potent and selective inhibitor of CETP that could provide an interesting new advance for the prevention and treatment of hypercholesterolemia.[6−8] We were interested in developing chemistry suitable for the preparation of kilogram quantities of **1** in an effort to support the exploration of its pharmacological properties. Our retrosynthetic analysis was centered around biaryl alcohol **2** that we hoped to prepare via a ruthenium-catalyzed direct arylation reaction. While we were actively involved in the optimization of this transformation, we observed an unprecedented and remarkable effect of a low-level impurity, γ-butyrolactone, found in the solvent used for this metal-catalyzed reaction. In the recent literature, we can find examples in which a beneficial effect of a low-level contaminant has been reported; however, the impurities were often found in the metal catalyst used. This was

† Dedicated to the memory of late Professor Keith Fagnou (1971−2009).

(1) For general references on Pd-catalyzed cross-coupling reactions, see: *Metal-Catalyzed Cross-Coupling Reactions*, 2nd ed.; Meijere, A. d., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

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(5) Vergeer, M.; Kastelein, J. J. P. *Nat. Clin. Pract. Cardiovasc. Med.* **2008**, *5*, 302.

(6) Pfizer entered a phase III clinical study with Torcetrapib. This study was halted in 2006 because of elevated blood pressure. Initial studies revealed that Anacetrapib could elevate HDL with no effect on blood pressure.

(7) O'Neill, E.; Sparrow, C. P.; Chen, Y.; Eveland, S.; Frantz-Wattley, B.; Milot, D.; Sinclair, P. J.; Ali, A.; Lu, Z.; Smith, C. J.; Taylor, G.; Thompson, C. F.; Anderson, M. S.; Cumiskey, A.; Rosa, R.; Strain, J.; Peterson, L. B. *J. Clin. Lipidol.* **2007**, *1*, 367.

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(9) For examples of Ni-contaminated Cr(II)-catalyzed coupling reactions, see: (a) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048. (b) Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644.

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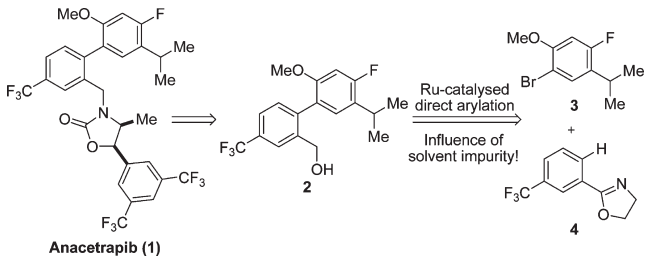


FIGURE 1. Retrosynthetic analysis of Anacetrapib (**1**).

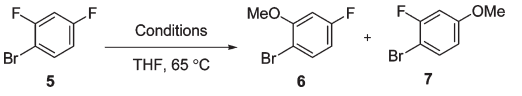
the case for the Cr(II)-catalyzed cross-coupling reaction reported by Kishi[9] and for the Fe-promoted coupling reaction described by Buchwald and Bolm.[10] Herein, we disclose how our findings with regard to the remarkable effect of the γ-butyrolactone impurity on the ruthenium-catalyzed direct arylation reaction allowed the development of a practical and chromatography-free synthesis of the biaryl core of **1** on a multikilogram scale.[11]

Biaryl alcohol **2** is a key intermediate in the preparation of Anacetrapib (**1**) as we envisioned a late stage displacement of its chloride by the corresponding oxazolidinone.[12] This building block would be obtained from a ruthenium-catalyzed direct arylation reaction between bromoanisole **3** and 2-aryloxazoline **4** (Figure 1). Both coupling partners would be prepared from readily available starting materials.

In the development of this synthetic sequence, significant consideration was placed on the selection of an appropriate approach to addressing the preparation of the biaryl core. While several traditional cross-coupling reactions were possible, the use of a directed arylation strategy appeared to be far more interesting. For the development of large scale synthesis of intermediates with commercialization potential, the opportunity to avoid functional group manipulation and/or activation steps is highly desirable. The cost associated with the various transformations and the bulk availability of the starting materials and the reagents used were also important discriminating factors in the selection of the synthetic path.

The synthetic efforts began with the preparation of 4-isopropyl-2-bromo-5-fluoroanisole (**3**). To access this intermediate, 1-bromo-2,4-difluorobenzene (**5**) was identified as being the starting material of choice. This building block is readily available in bulk quantity and is relatively inexpensive. From this starting material, a selective and high-yield S_NAr reaction between **5** and potassium methoxide was developed.[13] A significant improvement in selectivity was observed as the amount of methoxide used increased (Table 1). The improved selectivity arises from the favored consumption of the undesired isomer (**7**) that reacts faster in a second methoxide addition than the desired isomer (**6**).[14] This transformation

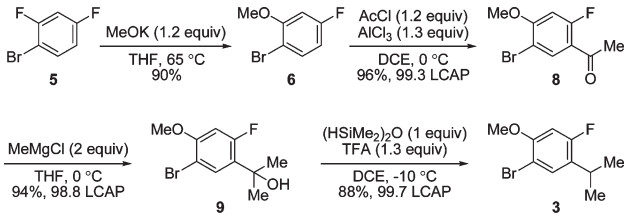
TABLE 1. S_NAr Reaction between 5 and Potassium Methoxide



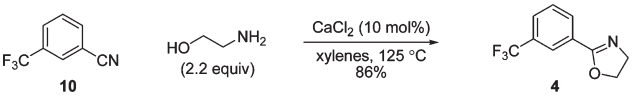
entry	MeOK (equiv)	time (h)	bis-OMe (%)	yield of **6**[a] (%)	**6**:**7** ratio
1	1.2	4	< 0.7	92[b]	18:1
2	5.0	18	9	88	65:1

[a]Assay yield measured by HPLC analysis. [b]The isolated yield after distillation was 90%.

SCHEME 1. Preparation of Aryl Bromide 3



SCHEME 2. Preparation of Oxazoline 4



provided access to 2-bromo-5-fluoroanisole in a 90% isolated yield in a 18:1 ratio.[15]

To introduce the isopropyl side chain, we developed a three-step sequence (Scheme 1). The acyl moiety was introduced via a Friedel−Crafts acylation of **6** in the presence of acetyl chloride and aluminum trichloride.[16] The acetophenone **8** was isolated in 96% yield as a white solid, and all the isomeric side products generated in the previous step were rejected during the crystallization [99.3 LCAP (liquid chromatography area percent)]. The carbinol **9** was obtained by addition of **8** to a cold solution of methylmagnesium chloride in THF. Under these conditions, a high level of conversion (99.8%) was achieved that obviated the use of an additive such as cerium trichloride. Following a cold hexane swish, the carbinol **9** was obtained in 94% yield as a white solid. Finally, the tertiary alcohol was reduced using tetramethyldisiloxane and TFA. Three low-level impurities were typically observed: the corresponding styrene and two isomeric dimers presumably formed via a carbocation intermediate. The formation of those impurities could be minimized by carefully keeping the reaction temperature below −5 °C. The dimers were easily rejected by distillation (from 0.7 to < 0.1 LCAP) as well as most of the siloxane byproduct. Finally, the oxazoline **4** was obtained from the calcium chloride-catalyzed condensation of 3-(trifluoromethyl)benzonitrile **10** and ethanolamine in xylene (Scheme 3).

With both coupling partners in hand, we set out to identify the optimal reaction conditions to access the biaryl core of Anacetrapib. Our efforts were initially inspired by an article reported by Oi, Inoue, and co-workers in which an efficient ruthenium-catalyzed cross-coupling reaction between oxazolines

(10) For examples of copper-contaminated Fe-catalyzed cross-coupling reactions, see: Buchwald, S. L.; Bolm, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 5586.

(11) Angelaud, R.; O'Shea, P.; Ouellet, S.; Roy, A. PCT Int. Appl. WO 2007136672, 2007.

(12) For the preparation of the oxazolidinone, see: Miller, R. A. PCT Int. Appl. WO 2008/082567, 2008.

(13) Ouellet, S. G.; Bernardi, A.; Angelaud, R.; O'Shea, P. D. *Tetrahedron Lett.* **2009**, *50*, 3776.

(14) The bis-addition product formed could easily be removed by fractional distillation to provide a highly enriched mixture of isomer **6**.

(15) After fractional distillation (90 °C, 3−5 Torr), the isomeric ratio was 18.5:1 (**6**:**7**) with 0.48% 1-bromo-2,4-dimethoxybenzene. These impurities were rejected during the crystallization of acylated product **8**.

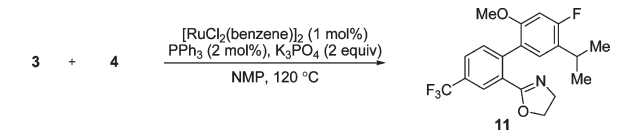
(16) Other Lewis acids such as $BiCl_3$, $Bi(OTf)_3$, $TFAA/H_3PO_4$, and $TiCl_4$ were tried without success.

and aryl bromide was described.[17] Initially, the reaction of bromoanisole **3** and oxazoline **4** was examined using 2.5 mol % $[RuCl_2(\mu^6\text{-}C_6H_6)]_2$ and 10 mol % PPh_3 in the presence of 2 equiv of K_3PO_4 in NMP at 120 °C for 20 h. Under these conditions, we were pleased to observe good conversion and a generally clean reaction profile. We next set out to evaluate each of the reaction parameters independently to identify the optimal reaction conditions. We first tested several ligands to determine that electron rich [such as $(Cy)_3P$], electron deficient [such as $(4F\text{-}C_6H_4)_3P$], or bidentate (such as dppf) ligands typically provided the coupled adduct in lower yields. The use of $[RuCl_2(p\text{-cymene})]_2$ was also evaluated but offered no significant advantages in terms of cost or reaction efficiency. While K_2CO_3 and Cs_2CO_3 were also found to be acceptable bases, the use of organic bases such as $i\text{-}Pr_2NEt$ or Et_3N failed to afford **10** in good yields. Finally, polar aprotic solvents such as NMP, DMA, and DMF[18] were found to be suitable for this transformation, while a less polar solvent such as toluene or xylene afforded the desired product in lower yields.

In the development of this catalytic process, it was very important to identify the best balance between reproducibility (or robustness) and low catalyst loading. While the optimized reaction conditions were highly reproducible at a higher catalyst loading (5 mol % Ru), we observed significant variability (30−99% conversion) when the catalyst loading was reduced to 0.5−1 mol % Ru. This variability was even more pronounced when we conducted this transformation on a multigram scale. We first suspected the agitation mode to be responsible for this notable lack of reproducibility, but side-by-side experiments in which mechanical and magnetic stirring were compared provided comparable results.[19] This was also consistent with the fact that the particle size of the K_3PO_4 used had a negligible impact on the reaction outcome. We observed a small effect associated with the heating rate and the order of addition of the various reagents. We typically observed a slightly higher level of conversion when a solution of the catalyst and ligand was added to a warm reaction mixture. This alone, however, did not explain the large variability that was observed. We noted the most significant variations in reaction efficiency when different lots of NMP were tested (the level of conversion would vary between 30 and 99%).

A careful examination of the different lots of solvent revealed the presence of a low-level impurity that was identified as being γ-butyrolactone.[20] We observed that the efficiency and reproducibility of the cross-coupling reaction were enhanced in the presence of an appreciable amount of γ-butyrolactone [complete conversion of the starting materials (Table 2, entry 1)]. On the other hand, reactions involving γ-butyrolactone-free NMP proceeded poorly (entry 2). This was confirmed with a control experiment in which γ-butyrolactone was added to a reaction mixture that previously failed (using lot B). In this case, we were able to fully restore the catalyst activity and observe a high level of conversion (entry 3). To address this reproducibility issue, we hypothesized that in the presence of K_3PO_4 and a trace amount of water, a certain concentration of carboxylate resulting from the hydrolysis of γ-butyrolactone could have been formed and acted as a soluble carboxylate source that enhanced the reactivity and/or stability of the ruthenium catalyst. In line with these observations, it was shown that highly efficient and reproducible reactions could be realized when a catalytic amount of potassium acetate was added to the reaction mixture (entries 4 and 5).[21,23]

TABLE 2. Optimization of the Ru-Catalyzed Direct Arylation Reaction between 3 and 4



entry	solvent (lot)[a]	additive	conversion (%)[b]
1	NMP (lot A)	−	>98
2	NMP (lot B)	−	30−50
3	NMP (lot B)		>98[c]
4	NMP (lot A)	AcOK[d]	>98
5	NMP (lot B)	AcOK[d]	>98

[a]NMP (lot A): contained 0.3−0.6% butyrolactone, detected by ^1H NMR. NMP (lot B): butyrolactone not detected by ^1H NMR. [b]Conversion measured by HPLC analysis. Reactions were repeated at least twice on a 5−20 g scale. [c]Butyrolactone (0.5 vol %) was added. [d]AcOK (10 mol %) was added.

Interestingly, most of the Ru-catalyzed direct arylation reactions reported use NMP as the optimal solvent.[22] In some cases, remarkable differences in reactivity were noted between NMP and other solvents that share very similar properties (such as DMF and DMA).[23] It is possible that the improved reaction profiles observed in NMP are in fact due to the presence of trace amounts of γ-butyrolactone that is known to be a common impurity found in NMP. Our hypothesis is further supported by recent publications describing the beneficial effect of carboxylate additives in direct arylation reactions. While this strategy was first developed in the context of palladium-catalyzed direct arylation reactions,[24] recent publications demonstrate its application in ruthenium-catalyzed reactions.[25] Moreover, recent reports by Ackermann described the utilization of carboxylic acid additives as co-catalysts to enhance the ruthenium-catalyzed arylation reaction

(17) Oi, S.; Aizawa, E.; Ogino, Y.; Inoue, Y. *J. Org. Chem.* **2005**, *70*, 3113.
(18) On a 1 mmol scale, >90% conversion was observed, and the reaction profile was slightly cleaner when NMP was used.
(19) These studies were conducted on a 5−10 g scale.
(20) γ-Butyrolactone is a common impurity found in NMP.
(21) Other additives such as TFA, pivalic acid, and 4-methylbenzoic acid were tested and were found to have a favorable effect on the reaction efficiency.
(22) For a recent review on metal-catalyzed direct arylation, see: Ackermann, L.; Vivente, R. In *Modern Arylation Methods*; Ackermann, L., Ed.; Wiley-VCH: Weinheim, Germany, 2009; pp 311−399. For selected examples of reactions developed in NMP, see: (a) Ozdemir, I.; Demir, S.; Çetinkaya, B.; Gourlaouen, C.; Maseras, F.; Bruneau, C.; Dixneuf, P. H. *J. Am. Chem. Soc.* **2008**, *130*, 1156. (b) Ackermann, L. *Org. Lett.* **2005**, *7*, 2123. (c) Oi, S.; Sakai, K.; Inoue, Y. *Org. Lett.* **2005**, *7*, 4009.
(23) (a) Ackermann, L.; Novák, P.; Vivente, R.; Hofmann, N. *Angew. Chem., Int. Ed.* **2009**, *48*, 6045. (b) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem., Int. Ed.* **2006**, *45*, 2619.
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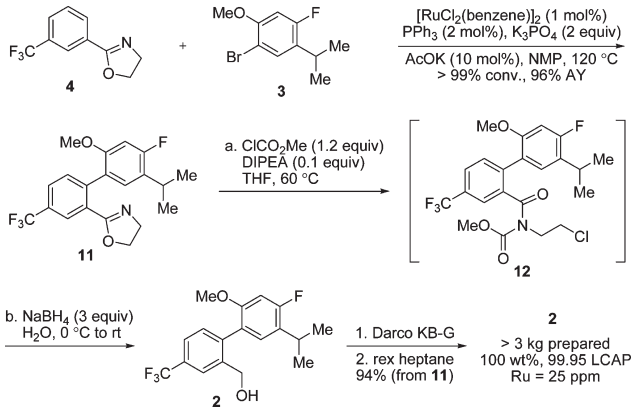
SCHEME 3. Preparation of the Biaryl Core of Anacetrapib



between several arenes and aryl halides. Under those conditions, the direct arylation reactions were found to be efficient in apolar solvent such as toluene[26] and polyethylene glycol.[27] More recently, the same author reported some mechanistic insight into the direct arylation reaction which led to the development of well-defined ruthenium(II) carboxylate catalysts.[28]

Using our robust catalyst system, the ruthenium-catalyzed direct arylation reaction was performed on 2.7 kg of **4** and 3.0 kg of **3** to yield 4.4 kg of biaryl **10** with an assay yield of 96% using only 1 mol % catalyst (Scheme 2). To the best of our knowledge, this is the first report describing a ruthenium-catalyzed direct arylation reaction to be successfully demonstrated on a multikilogram scale.[29]

To complete the synthesis of **2**, we developed a practical method to access the desired alcohol in one pot. Oxazoline **11** could be easily converted to the corresponding *N*-acylcarbamate **12** upon treatment with methyl chloroformate. Sodium borohydride reduction of the in situ-generated intermediate **12** afforded the desired alcohol **2** in good yield.[30] From **2**, Anacetrapib could easily be obtained using chemistry previously described.[31]

In summary, we observed a significant difference in the reaction efficiency and robustness of the ruthenium-catalyzed direct arylation reactions, which was attributed to the presence of γ-butyrolactone in NMP. This observation led us to consider the use of a carboxylate additive that allowed the reduction of catalyst loading while maintaining reproducibly high yields. This transformation was the key step in the efficient, practical, high-yield (65% overall yield), and chromatography-free seven-step synthesis of the biaryl precursor of Anacetrapib. To the best of our knowledge, this is the first example of a ruthenium-catalyzed direct arylation reaction to be successfully demonstrated on a multikilogram scale.

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(27) (a) Ackermann, L.; Novák, P.; Vicente, R.; Pirovano, V.; Potukuchi, H. K. *Synthesis* **2010**, 2245. (b) Ackermann, L.; Vicente, R. *Org. Lett.* **2009**, *11*, 4922.

(28) Ackermann, L.; Vicente, R.; Potukuchi, H. K.; Pirovano, V. *Org. Lett.* **2010**, *12*, 5032.

(29) (a) Jensen, M. S.; Hoerrner, R. S.; Li, W.; Nelson, P. D.; Javadi, G. J.; Dormer, P. G.; Cai, D.; Larsen, R. D. *J. Org. Chem.* **2005**, *70*, 6034. (b) Gauthier, D. J., Jr.; Limanto, J.; Devine, P. N.; Desmond, R. A.; Szumigala, R. H., Jr.; Foster, B. S.; Volante, R. P. *J. Org. Chem.* **2005**, *70*, 5938. (c) Cameron, M.; Foster, S. B.; Lynch, J. L.; Shi, Y.-J.; Dolling, U.-H. *Org. Process Res. Dev.* **2006**, *10*, 398.

(30) Bernardi, A.; Ouellet, S. G.; Angelaud, R.; O'Shea, P. D. *Tetrahedron Lett.* **2008**, *49*, 6707.

(31) For completion of the synthesis of Anacetrapib, see: Miller, R. A.; Cote, A. S. PCT Int. Appl. WO 2007/005572, 2007.

Experimental Section

Procedure Developed for the Kilogram Scale Ruthenium-Catalyzed Direct Arylation Reaction. A visually clean and dry 50 L reactor equipped with an overhead stirrer, a reflux condenser, a nitrogen inlet, and a temperature probe was charged with oxazoline **3** (2755.5 g) followed by anisole **4** (3065.7 g) and NMP (10 L predegassed with bubbling nitrogen for 60 min). The reaction mixture was degassed by bubbling nitrogen for 30 min, and then K_3PO_4 (4842.1 g) and KOAc (112.5 g) were charged followed by 2 L of degassed NMP (rinse). This suspension was degassed for an additional 60 min. The reaction mixture was then heated to 130 °C. A 5 L reactor was charged with degassed NMP (2 L) and triphenyl phosphine (29.92 g) and then degassed with bubbling nitrogen for 30 min at rt. The benzeneruthenium(II) chloride dimer complex (28.5 g) was then added, and this solution was degassed for an additional 30 min at room temperature. When the reaction mixture reached 130 °C, half of the ruthenium solution (1 L) was transferred, the reaction temperature was lowered to 110 °C, and the mixture was stirred at this temperature for 2 h before the addition of the second half of the ruthenium catalyst. Then, the reaction mixture was stirred at this temperature for an additional 7 h before being cooled to room temperature. To isolate the product, water (17 L) was added slowly (over 2.5 h) while the temperature was kept below 25 °C (at this point, an HPLC assay of the supernatant showed 1.6 g/L of product). The resulting slurry was then filtered through a filter pot, and the reaction flask was rinsed. The resulting solid was rinsed with an NMP/water mixture (1:1.5, 15 L), followed by water (40 L), and dried under a flow of nitrogen. Biaryl oxazoline **11** was obtained as a dark brown solid (4442.1 g, 93 wt %, 96% yield): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.59 (d, 1H, J = 8.0 Hz), 7.30 (d, 1H, J = 7.9 Hz), 6.99 (d, 1H, J = 8.6 Hz), 6.68 (d, 1H, J = 12.0 Hz), 4.49 (br, 2H), 3.73 (s, 3H), 3.21 (sept, 1H, J = 6.9 Hz), 1.95 (t, 1H, J = 6.2 Hz), 1.24 (d, 6H, J = 6.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.8, 159.9, 155.0 (d, J = 10.0 Hz), 140.5, 140.3, 130.9, 130.0 (q, J = 32.4 Hz), 129.1 (d, J = 7.2 Hz), 127.4, 127.3, 124.5 (q, J = 3.7 Hz), 124.2 (q, J = 272.1 Hz), 124.0 (d, J = 3.7 Hz), 123.8 (d, J = 3.4 Hz), 99.4 (d, J = 27.6 Hz), 62.7, 55.9, 26.6, 22.7; IR (neat) 2968, 1332, 1163, 1153, 1116, 1081, 1035, 831 cm^{-1}; HRMS (ESI) exact mass calcd for $[M + Na]^+$ ($C_{18}H_{18}F_4NaO_2$) m/z 365.1135, found m/z 365.1141.

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Supporting Information Available: Procedures, compound characterization data, and copies of spectra supporting structural assignments. This material is available free of charge via the Internet at http://pubs.acs.org.