JOC Article

Synthesis of Fluorinated β-Ketosulfones and *gem*-Disulfones by Nucleophilic Fluoroalkylation of Esters and Sulfinates with Di- and Monofluoromethyl Sulfones

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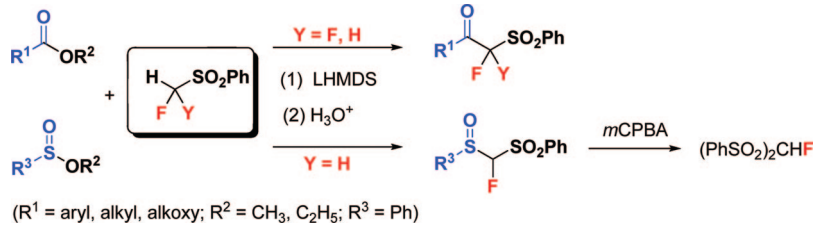

An efficient and practically useful method for the preparation of α-functionalized mono- and difluoro(phenylsulfonyl)methanes by using a nucleophilic fluoroalkylation methodology was developed. α,α-Difluoro-β-ketosulfones, α-monofluoro-β-ketosulfones, and α-fluoro disulfones were successfully prepared in excellent yields by nucleophilic fluoroalkylation of esters and sulfinates with $PhSO_2CF_2H$ and $PhSO_2CH_2F$ reagents.

Introduction

Nucleophilic fluoroalkylation, typically involving the transfer of a fluorine-bearing carbanion (R_f^-) to an electrophile, represents one of the major synthetic methods to synthesize organofluorine compounds.[1−5] During the past three decades, nucleophilic fluoroalkylation using organometallic reagents (R_fM) and organosilicon reagents (R_fSiR_3) have been extensively studied.[1,2] Among these reactions, the nucleophilic fluoroalkylation of carboxylic esters (to give fluoroalkyl ketones) generally needs well-controlled reaction conditions, and the yields vary widely.[6,7] Although nucleophilic perfluoroalkylation of Weinreb and morpholine amides with perfluoroalkyllithium reagents usually produces perfluoroalkyl ketones in high yields,[8] similar addition reactions to esters often result in the double-addition products (tertiary alcohols) as undesired byproduct.[6d,7a] Gassman and O'Reilly have shown that the nature of the products formed from the nucleophilic perfluoroalkylation of esters using fluoroorganometallic reagents was a function of both the structure of the ester and the reaction conditions.[6d] Prakash and coworkers reported a one-step conversion of various methyl esters to trifluoromethyl ketones using the Ruppert−Prakash reagent

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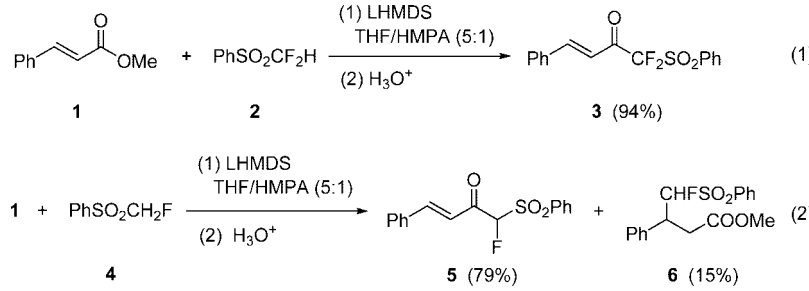
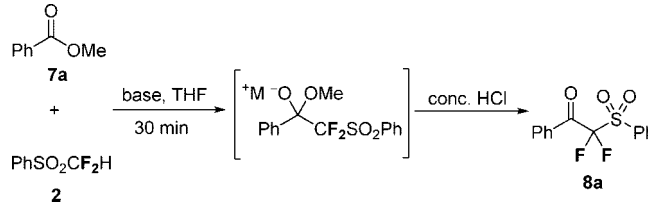
SCHEME 1. Nucleophilic Fluoroalkylations of Methyl Cinnamate 1



(Me_3SiCF_3) and a catalytic amount of fluoride initiator.[6a] The method has been further extended by Shreeve and co-workers using CsF as an initiator.[6b] Percy and co-workers found that the cerium mediated reaction between $(EtO)_2(O)PCF_2Li$ and various esters gave α,α-difluoro-β-ketophosphonates in moderate-to-good yields.[9] Recently, fluorinated sulfones such as $PhSO_2CF_2H$, $PhSO_2CF_2SiMe_3$, and $PhSO_2CH_2F$ have been extensively used as useful reagents in nucleophilic difluoromethylation, difluoromethylenation, and monofluoromethylation reactions.[3] However, both nucleophilic (phenylsulfonyl)difluoromethylation and (phenylsulfonyl)monofluoromethylation of esters have not been reported.

On the other hand, α-functionalized fluorinated sulfones such as $(PhSO_2)_2CHF$, $PhSO_2CHFCOPh$, and $PhSO_2CF_2$-COPh are of great interest in organic synthesis, since they can be used as "soft" fluoroalkylation reagents and also be subject to a range of transformations.[10] Currently, these α-functionalized fluorinated sulfones were commonly prepared by electrophilic fluorination with Selectfluor or an NFSI reagent (NFSI = *N*-fluorodibenzenesulfonimide)[10,11] or by oxidation of corresponding sulfides[12] or alcohols[13] through a two-step procedure. However, the electrophilic monofluorination procedure often leads to an undesired overfluorination (difluorination), and it is usually inconvenient to separate the mono- and difluorinated sulfones. Furthermore, electrophilic *gem*-difluorination of ketosulfones with an excess amount of Selectfluor sometimes only gives a moderate yield of difluorinated products.[14] Therefore, a more efficient and practical method for the preparation of various α-functionalized di- and monofluorinated sulfones is desired.

TABLE 1. Survey of Reaction Conditions for (Phenylsulfonyl)difluoromethylation



entry	base	molar ratio (**7a**:**2**:base)	additive[a]	temp (°C)	yield[b] (%)
1	LHMDS	1.2:1:1.2		−98	70
2	*t*-BuOK	1.2:1:1.2		−98	71
3	LHMDS	2:1:2		−98	70
4[c]	LHMDS	1.2:1:1.2		−98	0
5	LHMDS	1.2:1:1.2	HMPA	−98	82
6	LHMDS	1.2:1:1.2	HMPA	−78	75
7	LHMDS	2:1:2	HMPA	−98	92

[a] THF/HMPA = 10:1 (v/v). [b] Isolated yield. [c] 4-Benzoylmorpholine (instead of **7a**) was used as the electrophile.

Previously, in the course of our investigation of nucleophilic fluoroalkylation of α,β-enones with fluorinated sulfones, we found that for acylic α,β-enones, the hard or soft nature of the carbanions played a major role on the regioselectivity.[10f] When methyl cinnamate **1** was tested as a Michael acceptor, the regioselectivity of di- and monofluoromethylation are similar to the cases with α,β-enones, giving the fluorinated β-ketosulfones **3** and **5** as the major product, respectively (Scheme 1, eqs 1 and 2).[10f] These results encouraged us to develop a general procedure for the synthesis of fluorinated α-ketosulfones and *gem*-disulfones by nucleophilic fluoroalkylation of esters and sulfinates with $PhSO_2CF_2H$ and $PhSO_2CH_2F$ reagents.

Results and Discussion

We began our investigation with the goal to search for optimized reaction conditions for the preparation of α,α-difluoro-β-ketosulfones from difluoromethyl sulfone **2** (Table 1). First, lithium hexamethyldisilazide (LHMDS) was chosen as the base to generate $PhSO_2CF_2Li$ in situ from $PhSO_2CF_2H$ (**2**) at −98 °C. Thus, the reaction mixture of methyl benzoate **7a** (1.2 equiv) and $PhSO_2CF_2H$ (**2**) (1.0 equiv) was cooled to −98 °C and then treated with LHMDS (1.2 equiv). After 0.5 h, the reaction mixture was quenched with aqueous HCl solution at −98 °C. Simple workup and chromatography purification of the crude product gave α,α-difluoro-β-ketosulfone **8a** in 70% yield (entry 1). When *t*BuOK was used as the base, a similar result was obtained (entry 2). Change in the reactant ratio from 1.2:1:1.2 to 2:1:2 did not significantly affect the product yield (entries 1 and 3). Interestingly, when morpholine amide (4-benzoylmorpholine) was used as the electrophile, we did not obtain the carbinolamine or the corresponding ketone product

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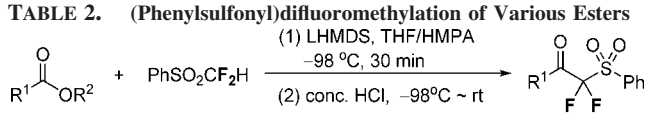
TABLE 2. (Phenylsulfonyl)difluoromethylation of Various Esters



7 2 8

entry	R^1	R^2	product	yield[a] (%)
1	Ph	CH_3	**8a**	92 (86)
2	4-Cl−C_6H_4	CH_3	**8b**	96 (88)
3	4-Br−C_6H_4	CH_3	**8c**	95 (87)
4	4-MeO−C_6H_4	CH_3	**8d**	85 (76)
5	CH_3	C_2H_5	**8e**	92 (84)
6	C_2H_5	C_2H_5	**8f**	87
7	CH_2=CH	C_2H_5	**8g**	0
8	PhC≡C	C_2H_5	**8h**	80 (72)
9	$COOC_2H_5$	C_2H_5	$PhSO_2CF_2C(OH)_2CO_2C_2H_5$ **8i**	93

[a] Isolated yield when the reaction was carried out on a 0.5−1.0 mmol scale. Number in parentheses refers to the isolated yield when the reaction was carried out on a 10−20 mmol scale.

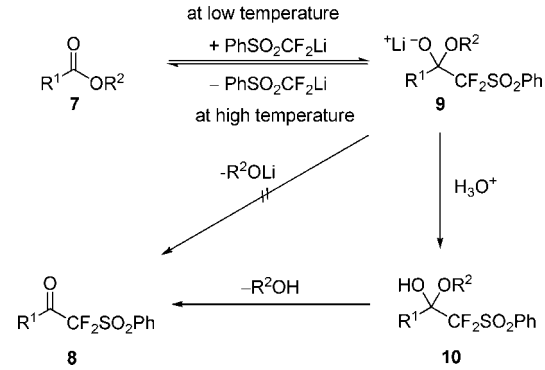
(entry 4). During the nucleophilic difluoromethylation of aldehydes and ketones with $PhSO_2CF_2H$,[15] it was found that the addition of hexamethylphosphoramide (HMPA) as a cosolvent could significantly improve the yields. Much to our delight, with HMPA as an additive, the reaction of **2** with **7a** and LHMDS in a molar ratio of 2:1:2 at −98 °C gave **8a** in 92% yield (entry 7). It seems that HMPA played an important role in the stabilization of the tetrahedral intermediate, the (phenylsulfonyl)difluoromethylated lithiated hemiketal. Furthermore, decreasing the temperature was found to be beneficial to the product yield, probably because of the enhanced stability of the lithiated hemiketal at a low temperature (entries 5 and 6).

By applying the optimized reaction condition (Table 1, entry 7), we turned our attention to the efficient synthesis of α,α-difluoro-β-ketosulfones from various esters, and the results are shown in Table 2. The reactions with different methyl and ethyl esters gave the corresponding ketones **8** in good-to-excellent yields (entries 1−6). When ethyl acrylate was used as an electrophile, no desired product was obtained, probably because of the high reactivity of this less hindered α,β-unsaturated ester toward LHMDS (entry 7). However, the reaction with ethyl 3-phenylpropiolate could afford the desired product **8h** in good yield, without the formation of Michael addition product (entry 8). For diethyl oxalate, the $PhSO_2CF_2^-$ anion selectively attacked one of the two ester groups, and the desired product **8i** was obtained in 93% yield as a hydrate form after acidic quenching (entry 9). As shown in Table 2, this preparative procedure was able to be scaled up with high product yields.

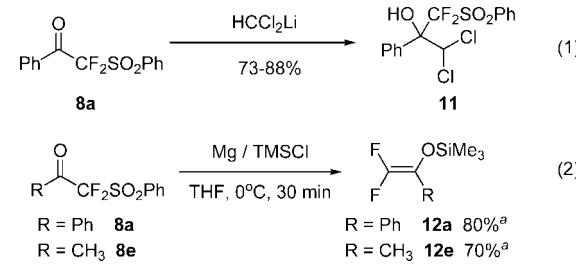
It should be noted that in all cases that no double addition product (that is, the bis[(phenylsulfonyl)difluoromethyl]-substituted carbinol) was observed. This suggests that before acidic quenching, the decomposition of the tetrahedral intermediate **9** to β-ketosulfones **8** via loss of R^2OLi was not occurring (Scheme 2). β-Ketosulfones **8** was likely formed from the dealcoholation of hemiketal intermediate **10**, which was formed during acidic quenching of **9**.

As one of the highly useful fluorinated building blocks, α,α-difluoro-β-ketosulfones can undergo many organic transformations. For example, treatment of the ketosulfone **8a** with dichloromethyllithium in THF at −98 °C in the presence of HMPA afforded dichlorohydrin **11** in good yield, which can

SCHEME 2. Proposed Mechanism for (Phenylsulfonyl)difluoromethylation of Esters



SCHEME 3. Various Transformations of 8[a]



[a] Determined by ^{19}FMR using $PhCHF_3$ as an internal standard.

act as a precursor for the synthesis of difluoromethyl substituted tri- and tetrasubstituted oxiranes and tetrasubstituted alkenes[16] (Scheme 3, eq 1). In addition, we found that magnesium metal-promoted reductive desulfonylation of the ketosulfones **8a** and **8e** in the presence of TMSCl afforded 2,2-difluoro enol silyl ethers **11a** and **11e** in 70−80% yields (Scheme 3, eq 2), which provides an alternative method for the preparation of 2,2-difluoro enol silyl ethers.[17]

Nucleophilic (phenylsulfonyl)monofluoromethylation of esters[18] with fluoromethyl phenyl sulfone **4** was also investigated. Reactions between **4** and esters in the presence of LHMDS readily took place, providing the corresponding α-fluoro-β-ketosulfones **13** in excellent yields (Table 3). Different from the above-mentioned difluoromethylation of esters, the monofluoromethylation was able to proceed smoothly even at −78 °C, and no additional HMPA was necessary to promote the formation of the lithiated hemiketals. However, in the case of carbonate, there was an equilibrium between the reactant and the lithiated hemiketal intermediate, and 2.0 equiv of diethyl carbonate was required for a complete consumption of the sulfone reagent **4** (Table 3, entry 8).

The efficient nucleophilic fluoroalkylation method was also extended to arylsulfinates. When excess methyl benzenesulfinate **14** (1.2 equiv) reacted with $PhSO_2CH_2F$ (**4**) in the presence of LHMDS at −78 °C, monofluorinated α-sulfonyl sulfoxide **15** was obtained as a mixture of two diastereomers in the ratio of 1:2 (Scheme 4). Subsequent oxidation of the sulfoxide **15**

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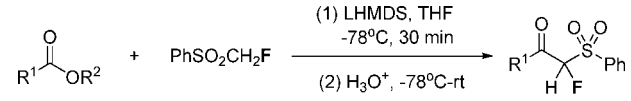
TABLE 3. (Phenylsulfonyl)monofluoromethylation of Various Esters

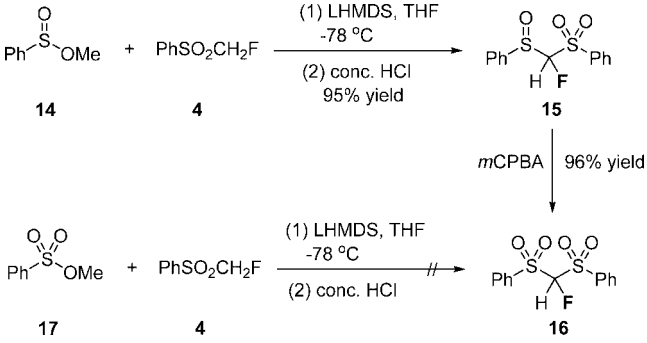


7 4 13

entry[a]	R^1	R^2	monofluoroproduct	yield[b] (%)
1	Ph	CH_3	**13a**	98
2	4-Cl−C_6H_4	CH_3	**13b**	97
3	4-Br−C_6H_4	CH_3	**13c**	92
4	4-MeO−C_6H_4	CH_3	**13d**	95
5	CH_3	C_2H_5	**13e**	96
6	C_2H_5	C_2H_5	**13f**	93
7	PhC≡C	C_2H_5	**13g**	94
8[c]	OCH_2CH_3	C_2H_5	**13h**	93

[a] Unless otherwise noted, the reaction was carried out with **7**/**4**/LHMDS = 1.2:1.0:1.2 on a 0.5−1.0 mmol scale. [b] Isolated yield. [c] Reactant ratio was **7**/**4**/LHMDS = 2:1:2.

SCHEME 4. Preparation of 16 by Monofluoromethylation of 14



14 4 15 17 4 16

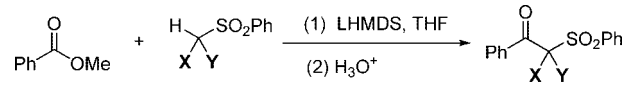
afforded fluorobis(phenylsulfonyl)methane **16** with 91% overall yield. This sulfination and oxidation procedure provides a highly useful and practical method for the preparation of α-fluoro disulfones such as **16**. It should be mentioned that compound **16** is an excellent and widely used monofluoromethide equivalent for the synthesis of a series of achiral and chiral monofluoromethylated compounds.[10]

In addition, we also attempted the nucleophilic monofluoroalkylation of benzenesulfonate **17** using **4** and LHMDS, but no desired α-fluoro disulfone **16** was formed (Scheme 4). The reaction between benzenesulfinate, $PhSO_2CF_2H$ (**2**), and LHMDS under the similar conditions was attempted but failed to give the desired difluorinated α-sulfonyl sulfoxide ($PhSO_2CF_2SOPh$).

Although the nucleophilic fluoroalkylation of esters with di- and monofluoromethyl sulfones is a useful method for the synthesis of fluorinated β-ketosulfones, reactions with chlorinated sulfones are rare.[19] For a comparison of the reactivity of different halogenated sulfone carbanions toward esters, we examined the reactions of mono- and dichlorinated sulfones with methyl benzoate. As shown in Table 4, monochlorinated sulfone **18** could give a moderate yield of α-chloro-β-ketosulfone product **19** (entry 3). However, dichlorinated sulfone **20** could not react with methyl benzoate **7a**, and the starting material **20** was recovered (see entry 4). The reactivity differences between

(19) We noticed that there is only one example reported on the nucleophilic addition of chlorinated sulfone carbanion to the carbonyl group of dimethyl chloromaleate with low yield. See: Makosza, M.; Nizamov, S.; Kwast, A. *Tetrahedron* **2004**, *60*, 5413–5421.

TABLE 4. Comparison of Fluorinated and Chlorinated Sulfones



7a

entry[a]	halogenated sulfone	product	yield[b] (%)
1	**2**: X = F, Y = F	**8a**	92
2	**4**: X = F, Y = H	**13a**	98
3	**18**: X = Cl, Y = H	**19**	50 (48)[c]
4	**20**: X = Cl, Y = Cl	**21**	0 (97)

[a] Reaction conditions: for entries 1 and 4, **7a**/sulfone/LHMDS = 2:1:2, THF/HMPA = 10:1, −98 °C; for entries 2 and 3, **7a**/sulfone/LHMDS = 1.2:1:1.2, −78 °C. [b] Isolated yield. Number in parentheses refers to the recovery yield of the unreacted sulfone. [c] The yield was determined by ^{1}H NMR analysis of the mixture of **18** and **19**.

halogenated sulfone carbanions toward esters may arise from the different stability of the lithiated hemiketals. It is expected that the chlorinated sulfone carbanions possess better leaving ability than the fluorinated ones, so the lithiated mono- or dichloromethylphenylsulfonyl substituted hemiketals would be less stable than the corresponding mono- and difluoromethylphenylsulfonyl substituted ones.

Conclusions

In conclusion, we have shown an efficient and practically useful method for the preparation of α-functionalized mono- and difluoro(phenylsulfonyl)methanes by using a nucleophilic fluoroalkylation methodology. α,α-Difluoro-β-ketosulfones, α-monofluoro-β-ketosulfones, and α-fluoro disulfones could be prepared in excellent yields by nucleophilic fluoroalkylation of esters and sulfinates with $PhSO_2CF_2H$ and $PhSO_2CH_2F$ as reagents. The fluorinated products are expected to be useful fluorinated building blocks, as exemplified by the conversion of α,α-difluoro-β-ketosulfones to the corresponding 2,2-difluoro enol silyl ethers promoted by magnesium metal in the presence of TMSCl. Efforts are underway to extend the scope of the fluorinated sulfones to fluorinated heteroaromatic sulfones and to apply these α-functionalized fluorinated sulfones for other transformations.

Experimental Section

General Procedure for the Preparation of α,α-Difluoro-β-ketosulfone 8: 2,2-Difluoro-1-phenyl-2-(phenylsulfonyl)ethanone (8a).[14] Under N_2 atmosphere, into a Schlenk tube containing methyl benzoate **7a** (136 mg, 1.0 mmol) and $PhSO_2CF_2H$ (**2**) (96 mg, 0.5 mmol) in THF−HMPA (2.5 mL/0.25 mL) at −98 °C was added dropwise 1.0 M LHMDS in THF (1.0 mL, 1.0 mmol). The reaction mixture was then stirred vigorously at −98 °C for 30 min, followed by adding concentrated aqueous HCl solution (1 mL) at this temperature. The reaction mixture was slowly warmed to room temperature and then extracted with EtOAc (10 mL × 3). The combined organic phase was dried over $MgSO_4$. After the removal of volatile solvents under vacuum, the crude product was further purified by silica gel column chromatography (10:1 PE/EtOAc v/v as eluent) to afford product **8a** (137 mg, 92% yield). White solid, mp 80−81 °C, 92% yield. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (t, J = 7.8 Hz, 2H), 7.64−7.73 (m, 3H), 7.82 (t, J = 7.5 Hz, 1H), 8.03 (d, J = 7.6 Hz, 2H), 8.18 (d, J = 7.6 Hz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −101.9 (s). ^{13}C NMR (75 MHz, $CDCl_3$): δ 116.5 (t, J = 299 Hz), 128.9, 129.6, 130.8, 130.9, 132.0, 132.6, 135.4, 136.0, 183.8 (t, J = 24 Hz). MS (ESI, m/z): 314.0 (M + NH_4^+), 319.0 (M + Na^+), 351.0 (M + MeOH + Na^+). Anal. Calcd for

$C_{14}H_{10}F_2O_3S$: C, 56.75; H, 3.40. Found: C, 56.70; H, 3.75. IR (KBr): 1703, 1594, 1449, 1350, 1272, 1143 cm^{-1}.

General Procedure for the Preparation of α-Monofluoro-*β*-ketosulfone 13: 2-Fluoro-1-phenyl-2-(phenylsulfonyl)ethanone (13a). Under N_2 atmosphere, into a Schlenk tube containing methyl benzoate **7a** (163 mg, 1.2 mmol) and $PhSO_2CH_2F$ (**4**) (174 mg, 1.0 mmol) in THF (5.0 mL) at −78 °C was added dropwise 1.0 M LHMDS in THF (1.2 mL, 1.2 mmol). The reaction mixture was then stirred at −78 °C for 30 min, followed by adding saturated HCl water solution (2 mL) at this temperature. The solution mixture was extracted with EtOAc (20 mL × 3), and the combined organic phase was dried over $MgSO_4$. After the removal of volatile solvents under vacuum, the crude product was further purified by silica gel column chromatography (4:1 PE/EtOAc as eluent) to afford product **13a** (273 mg, 98% yield). White solid, mp 94−96 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.39 (d, J = 48 Hz, 1H), 7.45−7.61 (m, 4H), 7.62−7.76 (m, 2H), 7.87 (d, J = 7.6 Hz, 2H), 8.01 (d, J = 7.7 Hz, 2H). ^{19}F NMR (282 MHz, $CDCl_3$): δ −180.2 (d, J = 48 Hz, 1F). ^{13}C NMR (100 MHz, $CDCl_3$): δ 100.1 (d, J = 233 Hz), 128.8, 129.4, 129.7 (d, J = 3.0 Hz), 129.8 (d, J = 1.5 Hz), 133.9, 134.6, 135.0, 135.3, 186.5 (d, J = 18 Hz). MS (ESI, *m*/*z*): 295.9 ($M + NH_4^+$).

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Supporting Information Available: Experimental details and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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