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Highly regioselective Pd-catalyzed allylic alkylation of fluorobis(phenylsulfonyl)methane

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ABSTRACT

A highly regioselective palladium-catalyzed allylic alkylation of fluorobis(phenylsulfonyl)methane has been studied. Using different allylic carbonates, a variety of terminal mono-fluoromethylated compounds were achieved in 85–99% yields with high regioselectivities.

Mono-fluoromethylated compounds are of great importance in the field of medicinal[1] and material[2] chemistry. Therefore, new synthetic methods for highly stereo-selective introduction of CFH_2 group into organic compounds, using convenient starting materials, are still desirable. Fuorobis(phenylsulfonyl)methane[3] (FBSM) has successfully been demonstrated as a synthetic equivalent of a fluoromethide species.[4] Using the fluorinated carbanion generated from FBSM, thermally unstable species,[4] as a nucleophile, transition metal such as palladium[4] and iridium[5] catalyzed allylic alkylations of allylic alcohol derivatives has attracted considerable attention since 2006. This type of the reactions,[6] which usually lead to a mixture of the linear product and the branch product, is one of the powerful methods for preparation of mono-fluoromethylated compounds. It is possible to control regioselectivity through adjusting catalyst system.[5] More recently, we have successfully developed a methodology for synthesis of mono-fluoromethylated branch product from allylation of FBSM catalyzed by iridium.[5] In addition, introduction of a fluorine atom into the aliphatic moiety of liquid crystal compounds dramatically leads to the change of the physical property.[7,2c] We envision using allylic alkylation of FBSM to synthesize mono-fluoromethylated linear compounds. Herein, we report Pd-catalyzed allylic alkylation of mono-substituted allylic alcohol derivatives with FBSM and its potential in synthesis of liquid crystal compounds with a mono-fluorinated aliphatic group.

We began our investigations with a reaction of (*E*)-cinnamyl methyl carbonate (**1a**) with **2a** in the presence of 2 mol % of $Pd(OAc)_2$[8] and 4 mol % of DPPE[9] in THF at room temperature. To our delight, after 36 h, a mixture of the linear product (**3a**) and the branched product (**4a**)[2] was obtained in 91% yield with a ratio of **3a**/**4a** in 99/1 (entry 1). The use of 4 Å MS led to somewhat the improvement of the yield but long reaction time (36 h) (entry 2). When Cs_2CO_3 was employed as a base, both the rate and yield were improved (entry 3). Encouraged by these, a series of bases such as K_3PO_4, K_2CO_3, DBACO, BSA, and DBU were screened. Interestingly, all of Cs_2CO_3, K_3PO_4, K_2CO_3, and BSA gave the excellent results without significantly influencing the regioselectivity (entries 4–6). However, DBASO gave only 15% yield and DBU could not promote the reaction (entries 7–8). Consequently, we chose K_2CO_3 as the suitable base since it is more economic. Loading $Pd(OAc)_2$ was decreased from 2% to 1.5%; the yield was reduced as well (entry 10). Notably, this reaction could not proceed in the absence of DPPE, thus, the ligand DPPE is required to assist this AAA reaction (entry 11). Furthermore, other solvents including DCM and toluene were screened and we found that DCM gave 86% of **3a** along with **4a** with an excellent regioselectivity but longer reaction time (entry 12). Both THF and toluene resulted in excellent yield and high regioselectivity (entry 5 vs entry 13). THF was chosen as the suitable solvent because of the economic reason and convenient workout.

With the optimal reaction conditions listed in entry 5 of Table 1, we further explored the scope of this finding and the preliminary results were demonstrated in Table 2. All allyl methyl carbonates including aliphatic, phenyl, aromatic with an electronic-donating

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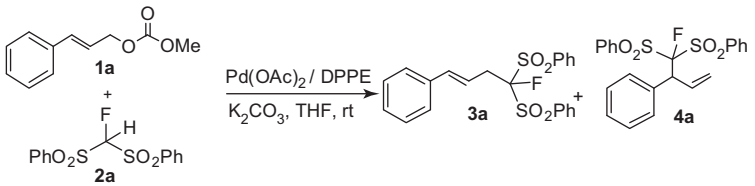
Table 1
Optimizing reaction conditions for Pd-catalyzed allylation of fluorobis(phenylsulfonyl)methane (FBSM)[a]

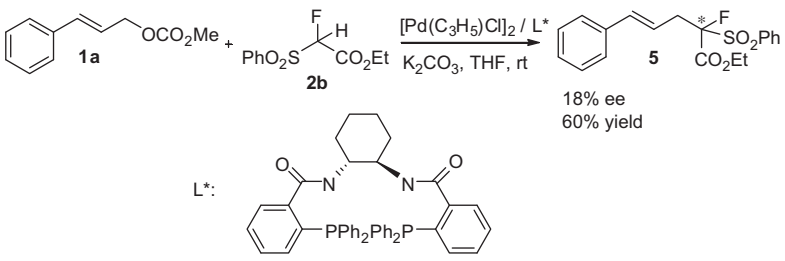


Entry	Base	Cat. loading (%)	Solvent	*t* (h)	Yield[b] (%)	**3a**/**4a**[c]
1	—[d]	2	THF	36	91	>99/1
2[e]	4 Å MS	2	THF	36	98	>99/1
3	Cs_2CO_3	2	THF	0.5	95	>99/1
4	K_3PO_4	2	THF	0.5	99	>99/1
5	K_2CO_3	2	THF	0.5	96	>99/1
6	BSA	2	THF	0.5	99	>99/1
7	DBACO	2	THF	10	15	>99/1
8	DBU	2	THF	10	NR	—
9	K_2CO_3	2	THF	0.5	94	>99/1
10	K_2CO_3	1.5	THF	6	86	>99/1
11[f]	K_2CO_3	2	THF	24	NR	—
12	K_2CO_3	2	DCM	10	94	>99/1
13	K_2CO_3	2	Toluene	0.5	99	>99/1

[a] Reaction conditions: 2 mol % $Pd(OAc)_2$, 4 mol % DPPE, 100 mol % of **1a**, 100% of base and 105 mol % **2a** at room temperature.
[b] Isolated yields.
[c] Determined by ^{19}F NMR.
[d] No base was added.
[e] 100 mg 4 Å MS were used.
[f] No ligand was employed.

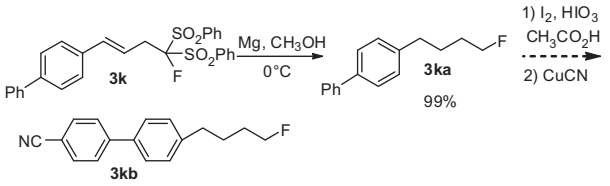
or electronic-withdrawing group, and heterocyclic substrates gave the corresponding linear product in excellent yield with high regioselectivity (entries 1–11, Table 2). Notably, ethyl 2-fluoro-2-(phenylsultonyl)acetate **2b** in racemic form was used instead of FBSM **2a** under the optimized conditions and it also gave the corresponding linear product **3l** in 85% yield with a ratio of **3l**/**4l** in 99/1 (entry 12).

Attempt to study on Pd-catalyzed asymmetric alkylation (AAA) of **2b** in racemic form, a combination of $[Pd(C_3H_5)Cl]_2$ and Trost's ligand was employed as a catalyst and this AAA reaction of **2b** was conducted under a similar condition. As a result, compound **5** was obtained in 60% yield with 18% ee (Eq. 1). The detailed studies on Pd-catalyzed AAA of **2b** are currently under way.



(1)

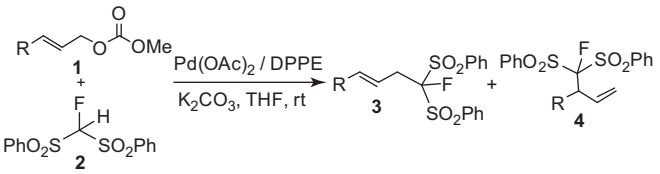
To explore the synthetic utility of the product obtained, a representative example was illustrated in Eq. 2. The phenylsulfonyl groups and double bond on **3k**[10] were readily removed and reduced in one-pot by using activated magnesium[11] and **3ka**[10] was produced in 99% yield.[3] Also, **3ka** may be converted into **3kb** according to the known procedure.[12] Compared with a known liquid crystal compound 4′-butylbiphenyl-4-carbonitrile,[13] **3kb** may exhibit good physical property of liquid crystal (Eq. 2).



(2)

In conclusion, we have developed a convenient method for preparation of mono-fluoromethylated compounds via a highly regioselective palladium-catalyzed alkylation of FBMS with various allyl methyl carbonates. This method will be able to apply to synthesize liquid crystal compounds containing terminal mono-fluorinated aliphatic group.

Table 2
Regioselective Pd-catalyzed allylations of FBSM with allyl methyl carbonates[a]



Entry	R	NuH	Product	Yield[b] (%)	**3**/**4**[c]
1	Ph	**2a**	**3a**	96	>99/1 (99/1)[e]
2	3-MeOC$_6$H$_4$	**2a**	**3b**	99	>99/1
3	4-MeOC$_6$H$_4$	**2a**	**3c**	99	>99/1
4	4-MeC$_6$H$_4$	**2a**	**3d**	99	>99/1
5	4-BrC$_6$H$_4$	**2a**	**3e**	95	>99/1
6	3-CF$_3$C$_6$H$_4$	**2a**	**3f**	93	>99/1
7	2-ClC$_6$H$_4$	**2a**	**3g**	90	>99/1
8	4-ClC$_6$H$_4$	**2a**	**3h**	99	>99/1
9	2-Thienyl	**2a**	**3i**	99	>99/1
10	Cyclohexyl	**2a**	**3j**	96	>99/1
11	4-PhC$_6$H$_4$	**2a**	**3k**	99	>99/1
12	Ph	**2b**[d]	**3l**	85	>99/1
13	Me	**2a**	**3m**[g]	86	84/16 (88/12)[f]

[a] Reaction conditions: 2 mol % Pd(OAc)$_2$, 4 mol % DPPE, 105 mol % of **1**, 100 mol % K_2CO_3, and 100 mol % **2** at room temperature.
[b] Isolated yields.
[c] Determined by ^{19}F NMR.
[d] Compound **2b** was used instead of **2a** in this case.
[e] Determined by HPLC.
[f] Determined by ^{1}H NMR.
[g] A mixture of (*E*)-isomer and (*Z*)-isomer in a ratio of 91/9 determined by ^{1}H NMR.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.11.132.

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8. (a) [Pd(allyl)Cl]$_2$ was also tested as a catalyst in this AAA reaction and it lad to the formation of the allyl by-product. In the process of our investigation, an example of Pd(PPh$_3$)$_4$ -catalyzed allylic alkylation of FBSM was reported by the group of Jinbo Hu.; For details, see: (b) Ni, C.; Hu, J. *Tetrahedron Lett.* **2009**, *50*, 7252–7255.
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10. (a) Typical procedure for the preparation of **3k**. To a mixture of allylic carbonates **1k** (0.21 mmol, 105%), FBSM **2a** (0.2 mmol, 100%), Pd(OAc)$_2$ (0.02 mmol, 2%) and DPPE (0.04 mmol, 4%) in dry THF (2 mL) was added K_2CO_3 (0.2 mmol, 100%), and the mixture was stirred at room temperature under Ar$_2$ atmosphere. After completion of the reaction, the reaction mixture was filtered through a core with kieselguhr using methylene dichloride as an eluent. Then the filtrate was concentrated and purified by flash chromatography with silica gel (PE/EtOAc = 5:1) to give the desired product, *(E)-4-(4-fluro-4,4-bis(phenylsulfonyl)but-1-enyl)biphenyl* (**3k**). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.93 (d, J = 8.4 Hz, 4H), 7.70–7.61 (m, 2H), 7.61–7.24 (m, 13H), 6.37 (d, J = 15.8 Hz, 1H), 6.01 (dt, J = 7.2 Hz, 15.6 Hz, 1H), 3.36 (dd, J = 6.9 Hz, J = 18.0 Hz, 2H). ^{13}C NMR (75 MHz, CDCl$_3$) δ 140.6, 140.4, 135.6, 135.3, 135.2, 130.9, 130.8, 129.0, 128.7, 127.3, 127.1, 126.8, 117.8 (d, J = 6.5 Hz), 114.7 (d, J = 265.7 Hz), 33.9 (d, J = 18.0 Hz). ^{19}F NMR (282 MHz, CDCl$_3$) δ −141.9 (dd, J = 12.1 Hz, J = 16.3 Hz). MS (ESI, m/z): 529.1 (M+Na$^+$). HRMS (EI): calcd for $C_{28}H_{23}FO_4S_2$ (M$^+$) 506.1022, found 506.1027. IR (KBr): 3526, 3060, 3030, 1484, 1446, 1346, 1310, 1150, 1076, 965, 752, 728, 628 cm^{-1}.
(b) *Typical procedure for the synthesis of* **3ka**: **3k** (73.1 mg, 0.14 mmol), Mg (69 mg, 2.88 mmol), and MeOH (3 mL) was added in a dry Schlenk tube under argon atmosphere. The reaction mixture was stirred overnight at room temperature. When **3k** was fully consumed, monitoring by TLC, the reaction was quenched with sat. NH$_4$Cl aq and extracted with Et$_2$O (4 × 10 mL). The combined organic phase was washed with brine, dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (PE/EtOAc = 1/10) to give *4-(4-fluorobuty)biphenyl* (**3ka**) (31.6 mg, 99% yield) as yellow liquid. ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.55 (dd, J = 18.5, J = 7.5 Hz, 4H), 7.42 (t, J = 7.2 Hz, 2H), 7.34–7.24 (m, 3H), 4.47 (dt, J = 47.4 Hz, J = 5.7 Hz, 2H), 2.70 (t, J = 6.9 Hz, 2H), 1.88–1.65 (m, 4H). ^{13}C NMR (151 MHz, CDCl$_3$) δ 141.10, 141.06, 138.80, 128.82, 128.71, 127.09, 127.02, 127.00, 84.00 (d, J = 163.5 Hz), 35.04, 30.11, 27.00 (d, J = 5.2 Hz). ^{19}F NMR (282 MHz, CDCl$_3$) δ −218.17 (tt, J = 47.4 Hz, J = 25.4 Hz). MS (EI, m/z): 228. HRMS (EI): calcd for $C_{16}H_{17}F$ (M$^+$) 228.1314, found 228.1316. IR (KBr): 3443, 3021, 2928, 2852, 1486, 1383, 1260, 1005, 836, 763, 695.
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