

Catalytic Enantioselective Fluorination of α -Cyanosulfones in the Presence of Chiral Palladium Complexes

Bo Kyung Kwon, Joo Yang Mang, and Dae Young Kim*

Department of Chemistry, Soonchunhyang University, Asan, Chungnam 336-745, Korea. *E-mail: dyoung@sch.ac.kr
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Chiral sulfonyl compounds are gaining an increasing importance in medicinal chemistry since they are considered as mimics of the carbonyl moieties in the transition state.¹ α -Substituted α -cyanosulfones would be versatile synthetic intermediates for the synthesis of β -amino sulfones.² Chiral organofluorine compounds containing a fluorine atom bonded directly to a stereogenic center have been utilized in studies of enzyme mechanisms and as intermediates in asymmetric syntheses.³ However, the use of optically active compounds containing a fluorine atom at a stereogenic carbon center is restricted by the limited availability of effective methods for the enantioselective construction of fluorinated quaternary carbon centers. Thus, the development of effective methodologies for the preparation of chiral organic fluorine compounds through C-F bond formation is still a highly desirable goal in synthetic organic chemistry.⁴ Since the first catalytic enantioselective fluorination by Togni,⁵ these reactions have been attracting much attention. Recently, several groups have reported catalytic enantioselective fluorination of active methines using chiral Lewis and organocatalysts.⁶⁻⁹ However, to the best of our knowledge, catalytic enantioselective fluorination of α -cyanosulfones has not been reported.

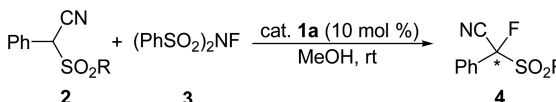
As part of research program related to the development of synthetic methods for the enantioselective construction of stereogenic carbon centers,¹⁰ we recently reported the catalytic enantioselective functionalization of active methines in the presence of chiral palladium(II) complexes.¹¹ In this communications, we wish to report the catalytic enantioselective electrophilic α -fluorination of α -cyanosulfones using chiral palladium complexes **1** (Fig. 1) which are air- and moisture-stable.

To determine suitable reaction conditions for the catalytic enantioselective fluorination of cyanoalkylsulfones, we initially investigated the reaction system with α -phenyl- α -cyanosulfones **2** and *N*-fluorobenzenesulfonimide (**3**, NFSI) in the presence of 10 mol % of chiral palladium(II) catalyst

in methanol at room temperature. We first examined the impact of the structure of α -phenyl- α -cyanosulfones **2** on enantioselectivities (Table 1, entries 1-4). The best results have been obtained with α -phenyl- α -cyano-(*p*-trifluoromethylphenyl)sulfone (**2c**).

In order to enhance the enantioselectivity, we examined a series of chiral diphosphine ligands in catalysts **1** (Table 2,

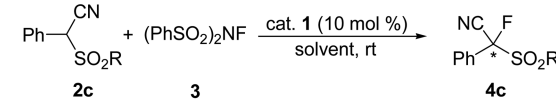
Table 1. Effect of the sulfonyl substituents of cyanosulfones **2**



Entry	2 , R	Time (h)	Yield (%) ^a	ee (%) ^b
1 ^c	2a , C ₆ H ₅ -	48	4a , 48	54
2	2b , <i>p</i> -CH ₃ C ₆ H ₄ -	36	4b , 70	77
3	2c , <i>p</i> -CF ₃ C ₆ H ₄ -	52	4c , 90	96
4 ^d	2d , -CH ₃	48	4d , nr	-

^aIsolated yield. ^bEnantiopurity was determined by HPLC analysis using with a chiralpak IC column. ^cThis reaction was carried out at 40 °C. ^dThis reaction was carried out at 60 °C.

Table 2. Optimization of reaction conditions



R = *p*-CF₃-C₆H₄-

Entry	Cat. 1	Solvent	Time (h)	Yield (%) ^a	ee (%) ^b
1	1a	MeOH	52	90	96
2	1b	MeOH	57	94	83
3	1c	MeOH	57	93	87
4	1d	MeOH	57	96	85
5	1e	MeOH	50	94	65
6	1f	MeOH	50	90	65
7	1a	H ₂ O	144	58	47
8	1a	EtOH	144	87	71
9	1a	<i>i</i> -PrOH	120	70	65
10	1a	EA	144	67	45
11	1a	acetone	144	75	27
12	1a	CH ₂ Cl ₂	144	81	13
13 ^c	1a	MeOH	24	98	97

^aIsolated yield. ^bEnantiopurity was determined by HPLC analysis using a chiralpak IC column. ^cThis reaction was carried out at 40 °C.

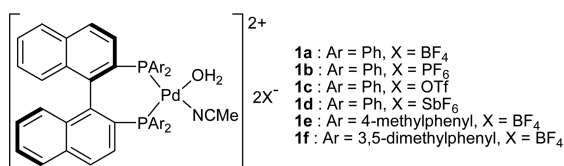


Figure 1. Structures of chiral palladium complexes **1**.

Table 3. Catalytic enantioselective fluorination of α -cyanosulfones **2**

Entry	2 , Ar	Time (h)	Yield (%) ^a	ee (%) ^b
1	2c , Ph	24	4c , 98	97
2	2e , <i>p</i> -FC ₆ H ₄	12	4e , 90	95
3	2f , <i>p</i> -ClC ₆ H ₄	12	4f , 85	95
4	2g , <i>p</i> -CH ₃ C ₆ H ₄	11	4g , 90	99
5	2h , <i>p</i> -CH ₃ OC ₆ H ₄	3	4h , 75	99
6 ^c	2i , <i>p</i> -(CH ₃) ₂ NC ₆ H ₄	72	4i , 85	87
7	2j , 2-naphthyl	13	4j , 90	95

^aIsolated yield. ^bEnantiopurity was determined by HPLC analysis using chiralpak IC (for **4c**, **4e**, **4h**, and **4j**), IA (for **4g** and **4i**) and chiralcel AS-H (for **4f**) columns. ^cThis reaction was carried out using 20 mol % of catalyst.

entries 1-6). By screening chiral palladium(II) complexes **1a-f**, we found that catalyst **1a** was the best catalyst for this enantioselective electrophilic fluorination, affording the corresponding product **4c** with 96% ee and 90% yield at room temperature (entry 1). Concerning the solvent, the use of protic polar solvents such as MeOH and EtOH gave the best results (entries 1 and 8), whereas the fluorination in ethyl acetate, acetone, and dichloromethane led to lower enantioselectivities (entries 10-12). Increasing the temperature to 40 °C in MeOH shortened the reaction time without compromising the yields and enantioselectivity (entry 13).

To examine the generality of the catalytic enantioselective fluorination of α -cyano sulfones **2** by using chiral palladium complex **1a**, we studied the fluorination of α -aryl- α -cyano- (*p*-trifluoromethylphenyl)sulfone derivatives **2** under optimum reaction conditions.¹² As it can be seen by the results summarized in Table 3, the corresponding α -fluorinated cyanosulfones **4** were obtained in moderate to high yields and excellent enantioselectivities (87-99% ee).

In summary, we have accomplished the efficient catalytic enantioselective electrophilic α -fluorination of various cyano-sulfones **2** with excellent enantioselectivity (up to 99% ee) in the presence of palladium complex **1a** as chiral catalyst. Current efforts are toward developing synthetic applications of this α -fluorination reaction.

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- Typical procedure:** To a stirred solution α -phenyl- α -cyano- (*p*-trifluoromethylphenyl)sulfone (**2c**, 32.5 mg, 0.1 mmol) and palladium catalyst **1a** (9.6 mg, 0.01 mmol) in MeOH (0.5 mL) was added NFSI (**3**, 37.8 mg, 0.12 mmol) at room temperature. The reaction mixture was stirred for 24 h at 40 °C. The resulting solution was concentrated and purified by flash chromatography to afford 33.6 mg (98%) of fluorinated adduct **4c**. white solid; mp 68-73 °C; $[\alpha]_D^{25} = -65.1$ ($c = 1.0$, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 7.57-7.53 (m, 2H), 7.65-7.62 (m, 1H), 7.69-7.67 (m, 2H), 7.94-7.91 (m, 2H), 8.18-8.16 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 99.7 (d, $J = 228.5$ Hz), 112.2 (d, $J = 29.9$ Hz), 122.8 (q, $J = 271.7$ Hz), 124.8 (d, $J = 21.3$ Hz), 126.6 (d, $J = 3.6$ Hz), 127.5 (q, $J = 5.8$ Hz), 129.0, 131.9, 132.6, 135.9, 137.4 (q, $J = 33.2$ Hz); HRMS (EI): m/z calcd for C₁₅H₁₀F₄NO₂S [M]⁺: 343.0290.; found 343.0287; HPLC (*n*-hexane:*i*-PrOH, 90:10, 254 nm, 1.0 mL/min) Chiralpak IC, $t_R = 5.22$ min (major), 6.23 min (minor), 97% ee.