DBFOX-Ph/metal complexes: Evaluation as catalysts for enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones

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Preliminary Communication

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Abstract

We examined the catalytic enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones **1** with *N*-fluorobenzenesulfonimide (NFSI) by DBFOX-Ph/metal complexes under a variety of conditions. After optimization of the metal salts, solvents and additives, we found that the fluoro-2-thiazolidinones **2** were obtained in good to high yields with moderate to good enantioselectivities (up to 78% ee) when the reaction was carried out in the presence of DBFOX-Ph (11 mol%), Ni(ClO$_4$)$_2$·6H$_2$O (10 mol%) and 2,6-lutidine (0 or 1.0 equiv) in CH$_2$Cl$_2$.

Background

Enantioselective electrophilic fluorination represents an important and straightforward strategy for C-F bond formation at a carbon stereocenter, providing easy access to chiral fluoro-organic compounds [1,2]. Due to the significance of chiral fluoro-organic compounds, such as fluorinated quinolones [3,4] and liquid crystals [5], in pharmaceutical and material sciences considerable effort has been dedicated to this issue for decades [6-17]. As a consequence, a variety of procedures have been developed to increase the yields and enantioselectivities of electrophilic fluorination reactions. Stoichiometric approaches based on cinchona alkaloid/Selectfluor® combinations [18-32], chiral ligand/metal-catalyzed [33-57] or organocatalytic [58-64] procedures for enantioselective fluorination are major advances in recent years. The discovery that chiral ligands/metals can catalyze electrophilic fluorination with conventional fluorinating reagents has had a large impact on synthetic organic chemistry, because of the availability of commonly used classes of ligands for asymmetric catalysis, such as, TADDOLs [37,39, 41,47], BINAPs [38,40,43,44,46,49,51,53,55-57] and bis(oxazoline) [33,34,36,42,45]. Of particular importance are
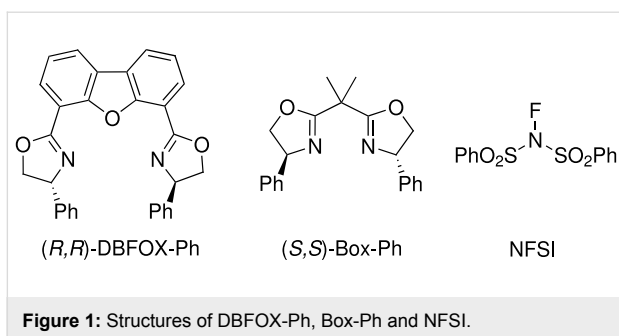
Figure 1: Structures of DBFOX-Ph, Box-Ph and NFSI.

BINAP ligands. Sodeoka et al. have used the latter ligands in asymmetric fluorination of a wide range of substrates, including β-keto esters, β-keto phosphonates, oxindoles [38,40,43,51,53, 56,57]. They have also recently reported the enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones with their extended catalytic system, $NiCl_2$-BINAP/R_3SiOTf-lutidine with high enantioselectivities [57]. This study is useful because, up until now, the fluorinated products obtained by Sodeoka's method have been prepared by diastereoselective methods [65-67]. Independently, our group has focused on the development of enantioselective fluorination and related reactions using bis(oxazoline) ligands, Box-Ph [(*S*,*S*)-2,2'-isopropylidene-bis(4-phenyl-2-oxazoline)] and DBFOX-Ph [(*R*,*R*)-4,6-dibenzo-furandiyl-2,2'-bis(4-phenyloxazoline)] [33,34,36]. As an extension of this study, we herein evaluate our DBFOX-Ph/metal catalysis for the enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones with N-fluorobenzenesulfonimide (NFSI) (Figure 1).
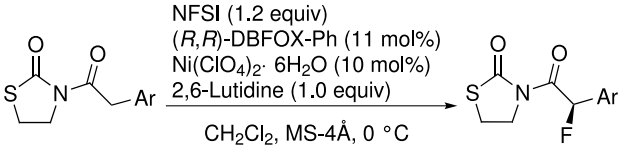
Results and Discussion

Our previous studies of the DBFOX-Ph/Ni(II)-catalyzed enantioselective fluorination of β-keto esters have shown that the optimal reaction conditions require NFSI as the fluorine source and a catalytic amount of $Ni(ClO_4)_2 \cdot 6H_2O$ in CH_2Cl_2 at room temperature. Therefore, we first attempted the reaction of **1a** with the same conditions and found that the desired fluorinated product **2a** was obtained in 42% yield with 69% ee (Table 1, entry 1). The reaction at higher temperature (40 °C) improved the yield to 62% with slightly lower enantioselectivity (63% ee, entry 2). The reaction time in these experiments was shortened by the addition of 1 equiv of 2,6-lutidine and **2a** was obtained in 87% yield with 66% ee at room temperature (entry 3). Both yield and selectivity were improved to 90% and 74% ee when the reaction was performed at 0 °C (entry 4). The highest ee value of **2a** was obtained at −20 °C, but resulted in a decrease in yield (24%, 79% ee, entry 5). Changing the metal salts did not improve the results (entries 6 and 7). The absolute stereochemistry of **2a** was determined by comparing the optical rotation and HPLC analysis with the literature values [57]. Although the enantioselectivities are moderate to good in these examples (63–79% ee), the results are quite impressive because the fluorination proceeds even in the absence of base (entries 1 and 2). That is, both $Ni(ClO_4)_2$-DBFOX-Ph (unary system, entries 1 and 2) and $Ni(ClO_4)_2$-DBFOX-Ph/lutidine (binary system, entries 3–6) are moderately effective in the enantioselective fluorination of **1a**. According to the report by Sodeoka using their $NiCl_2$-BINAP/R_3SiOTf-lutidine (trinary system, up to 88% ee obtained), the reaction requires both R_3SiOTf and

Table 1: Optimisation of the Conditions for DBFOX-Ph/Ni(II)-Catalysed Enantioselective Fluorination of 3-(2-Phenylacetyl)-2-thiazolidinone (**1a**)[a].

Run	Metal salt	2,6- Lutidine (equiv)	Temp (°C)	Time	Yield (%)	ee (%)
1	$Ni(ClO_4)_2 \cdot 6H_2O$	none	rt	6 d	42	69
2	$Ni(ClO_4)_2 \cdot 6H_2O$	none	40	4 d	62	63
3	$Ni(ClO_4)_2 \cdot 6H_2O$	1.0	rt	17 h	87	66
4	$Ni(ClO_4)_2 \cdot 6H_2O$	1.0	0	20 h	90	74
5	$Ni(ClO_4)_2 \cdot 6H_2O$	1.0	−20	4 d	24	79
6	$Ni(OAc)_2 \cdot 4H_2O$	1.0	rt	4 d	55	72
7	$Zn(OAc)_2$	1.0	rt	3 d	NR	-
8[b,c]	$Cu(OTf)_2$	1.0	0	2 d	NR	-
9[b]	$Ni(ClO_4)_2 \cdot 6H_2O$	1.0	0	2 d	33	15[d]

[a]For detailed reaction conditions, see Supporting Information File 1. Enantioselectivity was determined by chiral HPLC analysis. The absolute configuration of **2a** was determined by comparison with the optical rotation and HPLC analysis in the literature [57]. NR: No reaction. [b](*S*,*S*)-Box-Ph (11 mol%) was used instead of (*R*,*R*)-DBFOX-Ph. [c]Ether was used as solvent. [d](*S*)-**2a** was obtained.

Table 2: Enantioselective Fluorination Reaction of 3-(2-Arylacetyl)-2-thiazolidinones with NFSI Catalyzed by DBFOX-Ph/Ni(II)[a].

Entry	1	Ar	2	Time (h)	Yield (%)	ee (%)
1	**1a**	Ph	**2a**	20	90	74
2	**1b**	C_6H_4-*o*-OMe	**2b**	48	96	78
3	**1c**	C_6H_4-*m*-OMe	**2c**	24	94	66
4	**1d**	C_6H_4-*p*-OMe	**2d**	24	90	65
5	**1e**	C_6H_4-*o*-Me	**2e**	48	69	76
6	**1f**	C_6H_4-*m*-Me	**2f**	48	75	73
7	**1g**	C_6H_4-*p*-Me	**2g**	48	75	77
8	**1h**	C_6H_4-*p*-F	**2h**	48	60	62
9	**1i**	C_6H_4-*p*-Br	**2i**	48	77	56
10	**1j**	1-Naphthyl	**2j**	48	85	59
11	**1k**	2-Naphthyl	**2k**	48	90	60

[a]For detailed reaction conditions, see Supporting Information File 1. Enantioselectivity was determined by chiral HPLC analysis. The absolute configuration of **2a** was determined by comparison with the optical rotation and HPLC analysis in the literature [57]. Others were tentatively assigned by comparing the signs of their optical rotations to that of **2a**.

lutidine [57]. They mentioned in the paper that a binary system consisting of Ni(OTf)$_2$–binap complex and 2,6-lutidine failed to promote asymmetric fluorination. We also briefly attempted the fluorination of **1a** using the (*S*,*S*)-Box-Ph ligand instead of DBFOX-Ph. While the Box-Ph/Cu(OTf)$_2$ catalyst was not effective (run 8), the Box-Ph/Ni(ClO$_4$)$_2$·6H$_2$O catalyst gave the desired product **2a** in 33% yield with low enantioselectivity (15% ee, entry 9).

The DBFOX-Ph/Ni(ClO$_4$)$_2$·6H$_2$O catalysis for fluorination showed high generality for various 3-(2-arylacetyl)-2-thiazolidinones **1a**–**k** in good to high yields with moderate to good enantioselectivities. The results are summarized in Table 2. The fluorination reaction was not very sensitive to substitu-

tion in the position of the phenyl group and the desired products with methoxy or methyl groups at the *o*-, *m*-, or *p*-position of the benzene ring were obtained in 65–78% ee (entries 2–7). The reactions of fluoro or bromo-substituted **1h**, **i** and bulky-substituted **1j**, **k** afforded the desired products **2h**–**k** in good yields with slightly lower enantioselectivities (56–62% ee, entries 8–11).

The *R*-enantioselection of **2** can be explained by assuming an octahedral complex coordinated with a water molecule for DBFOX-Ph/Ni(II)/**1** as shown in Scheme 1. In the complex, the *Si* face is shielded by one of the phenyl groups of DBFOX-Ph so that NFSI approaches from the *Re* face of the substrates (Scheme 1). Since a major difference in ee values of **2** was not observed for the fluorination reaction of **1** with NFSI in the presence or absence of 2,6-lutidine (entries 1–3, Table 1), 2,6-lutidine presumably just accelerates the tautomerization of **1** to its enol form.

Conclusion

This research has demonstrated that DBFOX-Ph/Ni(II) catalysis can be used for the catalytic enantioselective fluorination of 3-(2-arylacetyl)-2-thiazolidinones with or without 2,6-lutidine to afford chiral 2-fluoro-2-arylacetate derivatives in good to high yields with moderate to good enantioselectivities of up to 78% ee. The Box-Ph ligand was not effective for this reaction. Our best ee value is slightly lower than that of Sodeoka's report [57]; this is presumably due to the low activity
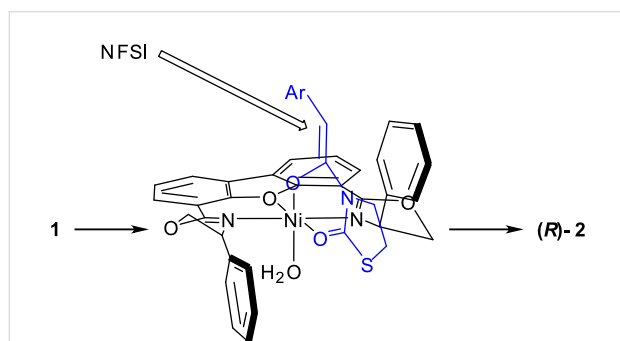
Scheme 1: Transition-State Structure for the DBFOX-Ph/Ni(II) Catalyzed Enantioselective Fluorination of **1** to **2**.

of our catalyst system which requires higher reaction temperature conditions (0 °C vs. −20 °C [57]). Racemization of the products **2** during the fluorination reaction was ruled out since no racemization was observed when **2a** was stirred overnight under the same fluorination conditions. Further studies to improve the enantioselectivity of DBFOX-Ph/metal catalysis in enantioselective fluorination are under way.

Supporting Information

Supporting Information File 1

Experimental methods. General methods, general procedure for the enantioselective catalytic fluorination, spectral data of **2**, copies of ^{1}H, ^{13}C and ^{19}F-NMRs and HPLC charts of **2**

[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-4-16-S1.doc]

Acknowledgments

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