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Catalytic Asymmetric Friedel–Crafts Reaction of Activated Phenols and 4-Oxo-4-arylbutenoates

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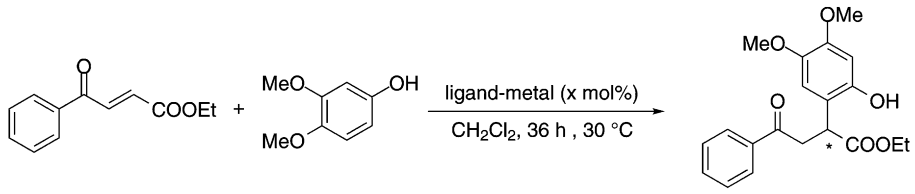
Abstract: A highly enantioselective Friedel–Crafts reaction of activated phenols with (*E*)-4-oxo-4-arylbutenoates has been developed with the *N,N′*-dioxide-scandium(III) complex as the catalyst. A variety of (*E*)-4-oxo-4-arylbutenoates were found to be suitable substrates for the reaction. The desired products were obtained in moderate to high yields (up to 98%) and excellent enantioselectivities (up to 97% *ee*).

Keywords: asymmetric catalysis; *N,N′*-dioxides; Friedel–Crafts reaction; phenols; scandium

The Friedel–Crafts alkylation of aromatic and heteroaromatic compounds is an important C–C bond forming process.[1] Over the past few years, several advances have been made in the asymmetric Friedel–Crafts alkylation of active aromatics, such as indoles, pyrroles, and naphthols.[2] Comparatively, the use of phenols as C-nucleophiles was less studied,[3] which is attributed to their relatively low reactivity. Based on the fact that the phenol unit occurs widespread in biologically active natural products and pharmaceutically useful molecules,[4] an expansion of the scope of phenols in this kind of reaction is of interest. Recently, Nagasawa[3a] et al. reported the catalytic asymmetric Friedel–Crafts alkylation of sesamol with nitroolefins using a bifunctional acyclic guanidine/bisthiourea organocatalyst with good results. Other organocatalysts were also used for the reaction of active phenol.[3b,c,d] Luo[3c] et al. employed binary-acid catalysis in the reaction of 2-methoxyphenol and β,γ-unsaturated α-keto esters, in which the addition of MgF_2 could improve the reactivity and enantioselectivity. However, the strong interaction of the unprotected hydroxy group of phenol with a metal center presents a difficulty in chiral Lewis acid catalysis. Limited research has been conducted in applying a chiral metal complex in the Friedel–Crafts reaction of phenols. Herein, we describe a readily available chiral *N,N′*-dioxide-$Sc(OTf)_3$ complex for the catalytic asymmetric Friedel–Crafts alkylation of phenol derivatives with (*E*)-4-oxo-4-arylbutenoates as option to address this issue.

In our previous study, the highly enantioselective Friedel–Crafts alkylation of indoles and pyrroles with α,β-unsaturated ketone derivatives could be achieved under chiral *N,N′*-dioxide-metal complex catalysis, as well as other types of asymmetric transformations.[5] Therefore, we initially investigated the reaction of 3,4-dimethoxyphenol (**2a**) with (*E*)-ethyl 4-oxo-4-phenylbutenoates (**1a**) promoted by metal complexes of the chiral *N,N′*-dioxide ligand **L1** derived from L-proline (Table 1, entries 1–4). The combination of $Mg(OTf)_2$ and $Y(OTf)_3$ with **L1** gave racemic products in poor yields (Table 1, entries 1 and 2). The use of **L1**-$Zn(BF_4)_2{\cdot}6H_2O$ catalyst afforded the desired product **3a** with 49% yield and 11% *ee* (Table 1, entry 3). $Sc(OTf)_3$ was found to be a suitable Lewis acid, providing the product **3a** in 65% yield and 43% *ee* (Table 1, entry 4). Encouraged by this result, we explored complexes of other *N,N′*-dioxide ligands (Figure 1) with $Sc(OTf)_3$. When the amide moiety of the *N,N′*-dioxide was replaced by aliphatic groups, the enantioselectivity as well as the reactivity increased dramatically (Table 1, entries 4–6). With ligand **L2** containing 1-adamantyl groups, 87% yield and 90% *ee* value were achieved (Table 1, entry 5). Interestingly, the product **3a** with the opposite configuration was obtained from the ligand **L3** with 2,6-diisopropylphenyl groups in moderate enantioselectivity (Table 1, entry 5 *versus* entry 6). Further optimization of the subunits of the *N,N′*-dioxide ligand showed that, with regard to the chiral backbone moiety, the L-proline-derived *N,N′*-dioxide achieved higher enantioselectivity and reactivity than the (*S*)-pipecolic acid- and L-ramipril-derived ones (Table 1, entry 5 *versus* entries 9 and 10). Steric hindrance of the ligand played a key role in enhanc-

Table 1. Optimization of the reaction conditions.[a]



1a **2a** **3a**

Entry	Ligand	Metal	X [mol%]	Yield [%][b]	*ee* [%][c]
1	L1	$Mg(OTf)_2$	5	14	0
2	L1	$Y(OTf)_3$	5	27	0
3	L1	$Zn(BF_4)_2{\cdot}6H_2O$	5	49	11 (*R*)
4	L1	$Sc(OTf)_3$	5	65	43 (*R*)
5	L2	$Sc(OTf)_3$	5	87	90 (*R*)
6	L3	$Sc(OTf)_3$	5	57	45 (*S*)
7	L4	$Sc(OTf)_3$	5	62	21 (*R*)
8	L5	$Sc(OTf)_3$	5	60	51 (*R*)
9	L6	$Sc(OTf)_3$	5	77	83 (*R*)
10	L7	$Sc(OTf)_3$	5	45	87 (*R*)
11[d]	L2	$Sc(OTf)_3$	5	92	92 (*R*)
12[d,e]	L2	$Sc(OTf)_3$	5	95	93 (*R*)
13[d,e]	L2	$Sc(OTf)_3$	1	54	92 (*R*)
14[d,e]	L8	$Sc(OTf)_3$	5	88	91 (*S*)

[a] Unless otherwise noted, the reactions were performed with **1a** (0.15 mmol), metal (0.005 mmol), *N,N′*-dioxide (0.005 mmol) under nitrogen in CH_2Cl_2 (1.0 mL) at 30 °C for 30 min, then **2a** (0.10 mmol) was added at 30 °C. The reaction mixture was stirred at 30 °C for 36 h.
[b] Isolated yield.
[c] Determined by chiral HPLC analysis (Chiralcel OD-H).
[d] Reaction was carried out with **L2**/$Sc(OTf)_3$ (1.2/1).
[e] The reaction was carried out in 0.3 mL CH_2Cl_2.

ing the reactivity and enantioselectivity, and the highly sterically demanding ligand **L2** turned out to be the best one. To our delight, when we changed the ratio of *N,N′*-dioxide **L2** with $Sc(OTf)_3$ to 1.2:1, and increased the reaction concentration, both the yield and the enantioselectivity were slightly increased (95% yield, 93% *ee*; Table 1, entry 12). However, when the catalyst loading was reduced from 5 to 1 mol%, there was a dramatic decrease in yield, with maintenance of the enantioselectivity (Table 1, entry 13). In addition, the corresponding enantiomer was easily obtained in good enantioselectivity and reactivity by using the complex *N,N′*-dioxide **L8**-$Sc(OTf)_3$ derived from D-proline (Table 1, entry 14). Note that the process is air and moisture tolerant.

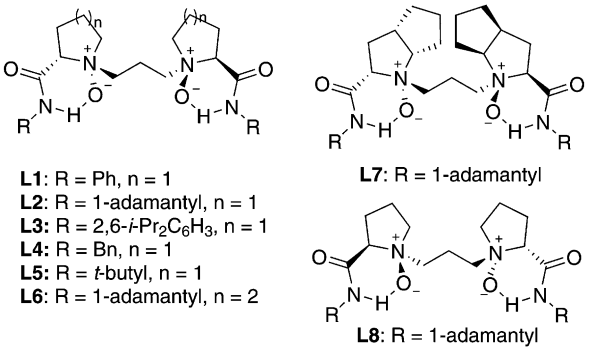
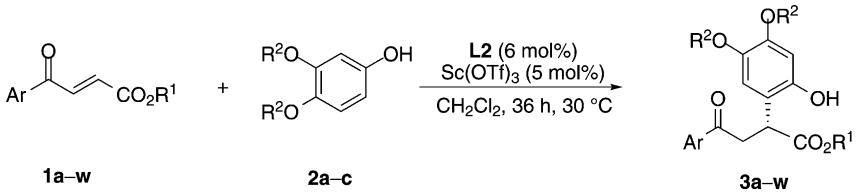


Figure 1. *N,N′*-dioxide ligands evaluated in this study.

Under the optimized conditions (Table 1, entry 12), a variety of (*E*)-4-oxo-4-arylbutenoates **1** and substituted phenols[6] **2** was investigated. First, the effect of the ester group of (*E*)-4-oxo-4-arylbutenoates was tested for the asymmetric Friedel–Crafts reaction of phenol. The ester groups had little influence on the enantioselectivity, and somewhat decreased yields were obtained for sterically hindered ester group (Table 2, entries 1–5). When the electron-donating group on the phenol was changed, the reactions went smoothly with good enantioselectivities and yields for methoxy-, ethoxy-, and isopropoxy-substituted phenols (Table 2, entries 1, 6, and 7). Then, a wide range of substituted (*E*)-ethyl 4-oxo-4-arylbutenoates **1** was tested in the asymmetric Friedel–Crafts reaction with phenol **2a**. Regardless of the electronic and steric nature, or the position of the substituents on the aromatic ring of **1**, the asymmetric Friedel–Crafts reaction proceeded smoothly. The desired products were furnished in high yields (78–98%) and enantioselec-

Table 2. Substrate scope for the asymmetric Friedel–Crafts reaction.[a]



Entry	Ar	R^1	R^2	Product **3**: Yield [%][b]	*ee* [%][c]
1	Ph	Et	Me	**3a**: 95	93 (*R*)
2	Ph	Me	Me	**3b**: 97	93 (*R*)
3	Ph	*i*-Pr	Me	**3c**: 78	92 (*R*)
4	Ph	*t*-Bu	Me	**3d**: 87	95 (*R*)
5	Ph	Bn	Me	**3e**: 96	92 (*R*)
6	Ph	Et	Et	**3f**: 93	91 (*R*)
7	Ph	Et	*i*-Pr	**3g**: 92	93 (*R*)
8	3-$MeOC_6H_4$	Et	Me	**3h**: 92	94 (*R*)
9	4-$MeOC_6H_4$	Et	Me	**3i**: 97	92 (*R*)
10	3,4-$(MeO)_2C_6H_3$	Et	Me	**3j**: 78	97 (*R*)
11	3-MeC_6H_4	Et	Me	**3k**: 93	91 (*R*)
12	4-MeC_6H_4	Et	Me	**3l**: 84	90 (*R*)
13	3,4-$Me_2C_6H_3$	Et	Me	**3m**: 87	93 (*R*)
14	2-FC_6H_4	Et	Me	**3n**: 88	94 (*R*)
15	4-FC_6H_4	Et	Me	**3o**: 93	89 (*R*)
16	4-BrC_6H_4	Et	Me	**3p**: 93	91 (*R*)
17	3-ClC_6H_4	Et	Me	**3q**: 95	89 (*R*)
18	4-ClC_6H_4	Et	Me	**3r**: 90	90 (*R*)
19	3,4-$Cl_2C_6H_3$	Et	Me	**3s**: 98	92 (*R*)[d]
20	3-$NO_2C_6H_4$	Et	Me	**3t**: 87	95 (*R*)
21	4-$NO_2C_6H_4$	Et	Me	**3u**: 92	94 (*R*)
22	2-furyl	Et	Me	**3v**: 86	88 (*R*)
23	2-thienyl	Et	Me	**3w**: 92	95 (*R*)
24[e]	Ph	Et	Me	**3a**: 87	89 (*R*)

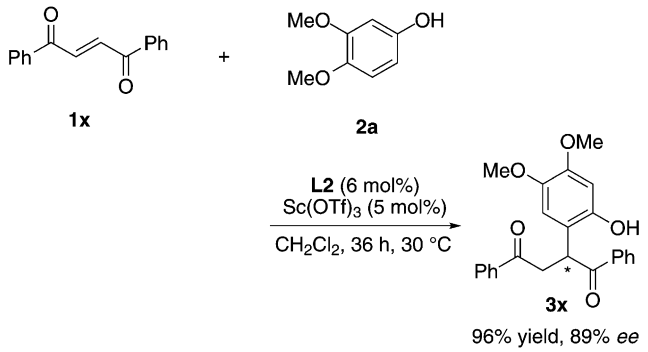
[a] Unless otherwise noted, the reactions were performed with **1** (0.15 mmol), and **2** (0.1 mmol) in the presence of **L2**/$Sc(OTf)_3$ (5 mol%, 1.2:1) in CH_2Cl_2 (0.3 mL) under nitrogen at 30 °C for 36 h.
[b] Isolated yield.
[c] Determined by HPLC analysis.
[d] The absolute configuration was determined to be *R* by X-ray crystallographic analysis, and the others were determined by comparison with the CD spectra.
[e] 3.5 mmol of substrate **2a** were used.

tivities (88–97% *ee*) (Table 2, entries 8–21). It is worth pointing out that the 3,4-dimethoxy-substituted (*E*)-ethyl 4-oxo-4-arylbutenoate **1j** afforded excellent enantioselectivity (97% *ee*), although the yield was slightly reduced in comparison with those of the mono-methoxy-substituted ones (Table 2, entry 10 *versus* entries 8 and 9). Notably, substrates bearing heteroaryl units proved to be competent candidates for the catalytic asymmetric Friedel–Crafts reaction (Table 2, entries 22 and 23). Additionally, the absolute configuration of the product **3s** was confirmed to be *R*. The others were also determined to be *R* in comparison with the Cotton effect in the CD spectra (see the Supporting Information for details).

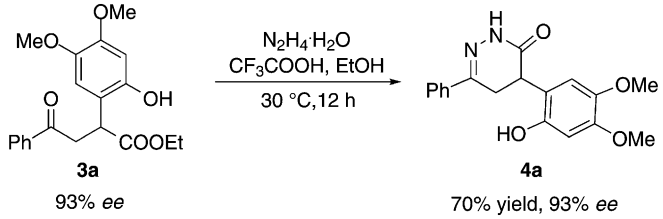
To our delight, (*E*)-1,4-diphenyl-2-butene-1,4-dione **1x** was also well tolerated in the current catalytic system, giving the adduct with 89% *ee* and 96% yield (Scheme 1).

The reaction provided an efficient approach to the synthesis of 6-phenyl-5-substituted-4,5-dihydro-3(2*H*)-pyridazinone **4a** (Scheme 2). In the presence of a catalytic amount of trifluoroacetic acid, **3a** reacted with hydrazine hydrate in EtOH at 30 °C for 12 h, giving the corresponding pyridazinone **4a** in good yield without any loss of the enantioselectivity (70% yield, 93% *ee*). The derived moiety represents a potentially useful biological agent[7] with activities such as antihypertension, platelet aggregation, as well as positive inotropic action.

In light of the X-ray structures of the product **3s**[8] and the *N,N′*-dioxide-Sc(III) complex,[9] a possible catalytic model for the Friedel–Crafts reaction of 3,4-



Scheme 1. The asymmetric Friedel–Crafts reaction of **1x** with phenol **2a**.



Scheme 2. The transformation of the product **3a**.

dimethoxyphenol with (*E*)-ethyl 4-oxo-4-arylbutenoates was proposed. As shown in Figure 2, the oxygens of the *N,N′*-dioxide moieties, and oxygens of the amides coordinate to the central Sc(III) metal in a tetradentate manner to form two six-membered chelate rings. The (*E*)-ethyl 4-oxo-4-arylbutenoates **2s** could coordinate to Sc(III) with the oxygen of the ketone moiety, in which the β-*Re* face is shielded by the nearby adamantyl group of the *N,N′*-dioxide **L2**. Then, 3,4-dimethoxyphenol could undergo bonding to the scandium complex in an upright position. The C-2 attacks 4-oxo-4-arylbutenoates **2s** preferably from the *Si* face, generating the *R*-configured product **3s**. The strong interaction of multiple O-donors of the ligand with the scandium complex overwhelms the coordination of phenol. Therefore, Lewis acid catalysis in the Friedel–Crafts reaction of phenol was achieved.

In summary, we have developed a direct, highly enantioselective catalytic asymmetric Friedel–Crafts reaction of 3,4-disubstituted phenols with (*E*)-4-oxo-4-arylbutenoates promoted by the *N,N′*-dioxide **L2**-$Sc(OTf)_3$ complex. Excellent enantioselectivities (up to 97% *ee*) and good yields (78–97%) were obtained by using a 5 mol% catalyst loading under mild reaction conditions. The corresponding products can be easily converted to pyridazinone derivatives. Further investigation of the catalyst system in the synthesis of biologically interesting molecules is ongoing.

Experimental Section

General Procedure for Catalytic Asymmetric Friedel–Crafts Reactions

A solution of *N,N′*-dioxide **L2** (3.4 mg, 0.006 mmol), scandium triflate (2.5 mg, 0.005 mmol) and (*E*)-ethyl 4-oxo-4-arylbutenoate **1** (0.15 mmol) in CH_2Cl_2 (0.3 mL) was stirred at 30 °C for 0.5 h. Subsequently, 3,4-disubstituted phenol **2** (0.10 mmol) was added. The reaction mixture was stirred at 30 °C for 36 h. The mixture was directly purified *via* flash chromatography (petroleum ether: ethyl ether = 3/1–2/1) on silica gel to afford the desired product.

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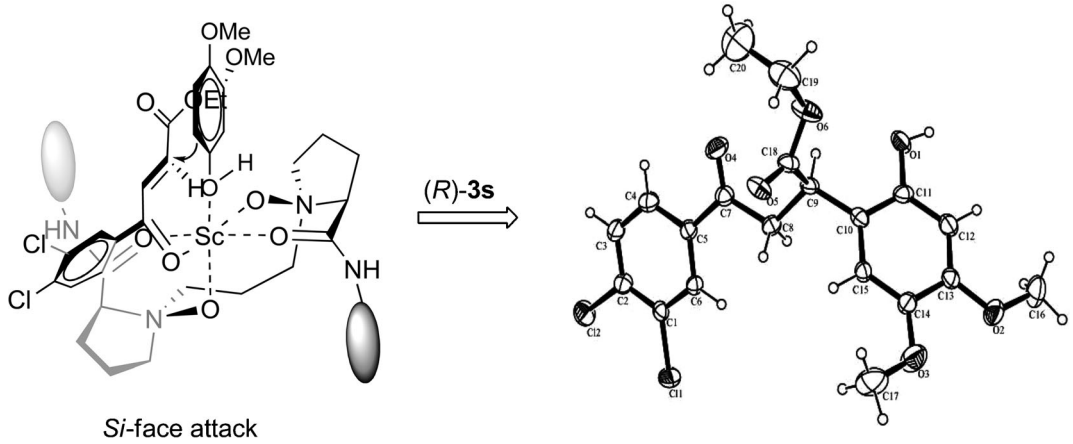

Figure 2. Proposed catalytic model and the X-ray structure of the product **3s**.

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