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Highly Enantioselective Synthesis of 2-Furanyl-hydroxyacetates from Furans via the Friedel−Crafts Reaction

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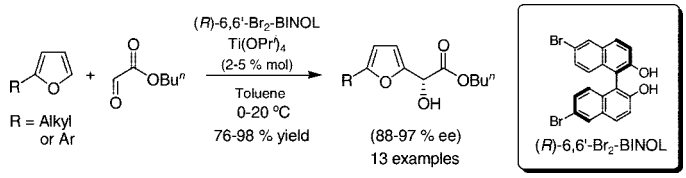
ABSTRACT



The Friedel−Crafts reaction of alkyl glyoxylates with variously substituted furans was found to be efficiently catalyzed under simple, undemanding conditions by a 6,6′-dibromo-BINOL/Ti(IV) complex with high enantioselectivity. The reaction afforded chiral substituted 2-furanyl-hydroxyacetic acid esters, compounds of high synthetic interest, in good yield and enantiomeric excess, in most examples in the range of 90−97%.

One of the most attractive approaches to the synthesis of chiral aromatic or heteroaromatic compounds having a stereogenic center in the benzylic position is the Friedel−Crafts (F−C) reaction with carbonyl compounds, imines, or some electron-deficient alkenes.[1] Of particular interest are enantioselective catalytic processes of this type leading to products having high optical purity. This chemistry has been intensively explored since about 2000, and interest in this field is still increasing. Most of the described enantioselective reactions concerning the F−C reactions utilize electron-rich aromatic and heteroaromatic compounds, in most cases aniline and indole derivatives,[2] catalyzed by chiral Lewis acids, usually with bisoxazoline or BINOL ligands, as well as various organocatalysts, e.g., based on BINOL-derived monophosphoric acids,[3] *Cinchona* alkaloids,[4] and MacMillan's imidazolidinones.[5]

We focused our attention on the asymmetric F−C reactions of furans with active aldehydes, namely, glyoxylates, including diastereoselective[6] and enantioselective approaches.[7] The products of this reaction, 2-furanyl-hydroxyacetic acid esters (**I**) (Scheme 1), are very interesting building blocks for the synthesis,[8] and after reduction to diols **II**, these synthons can be transformed under oxidizing conditions to linear (**III**) as well as cyclic products, e.g., dihydropyranones (**IV**) or dihydropyridones (**V**). Such an approach was utilized for the

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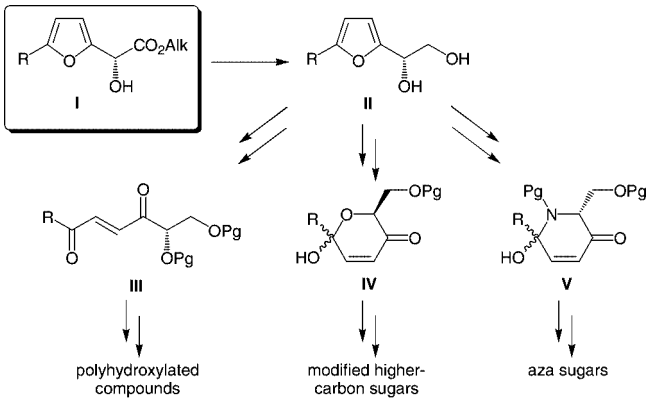
Scheme 1. Application of Furanyl α-Hydroxyacetates in the Synthesis



synthesis of multifunctional chain compounds,[9] higher-carbon sugars,[10] aza sugars,[11] and, e.g., in the synthesis of papulacandin D.[12]

The literature reports a few methods for the synthesis of optically pure 2-furanyl-hydroxyacetates or their derivatives by applying enzymatic resolution of racemic mixtures using lipases,[13] kinetic resolution using the Sharpless reagent,[14] reduction of furanyl-substituted 1,2-dicarbonyl compounds,[15] or addition of cyanides to furfurals.[16] The appropriate 1,2-diols of type **II** can be obtained via Sharpless asymmetric dihydroxylation of 5-substituted vinylfurans[12] or reduction of corresponding furanyl hydroxymethyl ketones,[17] and the simplest one (R = H) from the sugar derivatives (e.g., d-glucal).[18]

Compared to the above-mentioned methods, the synthesis of optically pure furanyl derivatives of type **I** or **II** via the F−C reaction directly from easily accessible furans and glyoxylates seems to be a very attractive and competitive approach. Until now, there is no effective, catalytic enantioselective method for the synthesis of 2-furanyl-hydroxyacetates directly from furans. Recently, we published a highly diastereoselective reaction of furans with chiral (1*R*,2*S*,5*R*)-8-phenylmenthyl glyoxylate promoted by magnesium bromide.[6b] Our previous attempts with chiral catalysts, e.g., salen−cobalt complexes, led to the F−C products of moderate enantioselectivity (up to 76% ee).[7] The catalytic enantioselective version of this reaction with bisoxazoline−copper complexes was also investigated by Jørgensen and coworkers,[19] although, in the case of reaction of 2-methylfuran (silvan) and ethyl glyoxylate, the enantioselectivity was low (45% ee),[20] in contrast to high ee values in the case of anilines (usually >80% ee). However, in the case of the F−C reactions of furans, other electrophiles, e.g., imines[3a,21] and α,β-unsaturated carbonyl compounds,[22] gave better results.

It was of interest for us to find an efficient and readily accessible catalytic system for the reaction of furans with glyoxylates. Jørgensen's[19] and our[7] studies in this field showed that bisoxazoline and salen metal complexes were not efficient enough in this case. We focused our attention on chiral BINOL-type ligands[23] and found that their complexes with Ti(IV), generated from BINOL and $Ti(OPr^i)_4$, were efficient catalysts for this reaction. The BINOL/Ti(IV) complexes were successfully introduced to asymmetric synthesis by Mikami[24] and Keck,[25] e.g., to ene, hetero-Diels−Alder, allylation,[26] and Mukaiyama aldol reactions. Mikami[27] also reported the first enantioselective F−C reactions of protected phenols with trifluoroacetaldehyde, catalyzed by the BINOL/Ti(IV) complexes. These complexes were also successfully applied in the reaction of glyoxylates with anilines by Ding et al.[28] and recently with indoles,[29] whereas the BINOL/Zr(IV) complexes were used in the reactions of α,β-unsaturated carbonyl compounds with indoles.[30]

Now we describe the first highly enantioselective Friedel−Crafts reaction of variously substituted furans **1a**−**m** with *n*-butyl glyoxylate (**2**). At the beginning, the reaction of **2** with 2-methylfuran (**1a**) was investigated (Scheme 2). Catalysts were generated in situ from either (*R*)-BINOL (**L1**) or (*R*)-6,6′-dibromo-BINOL (**L2**) and $Ti(OPr^i)_4$ in toluene at ambient temperature. In our study, the titanium complex of 6,6′-dibromo-BINOL (2 mol %) gave higher enantiose-

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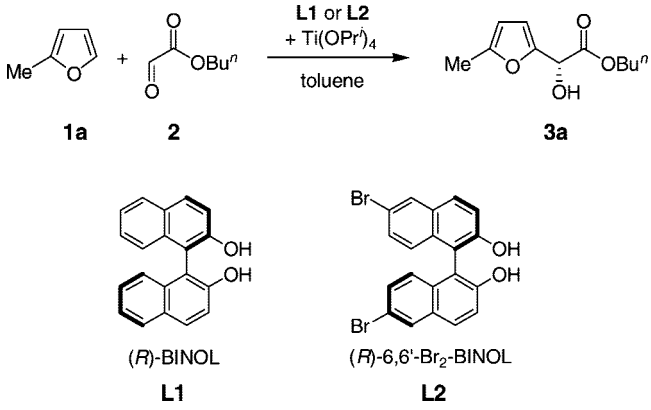
Scheme 2. Model Friedel−Crafts Reaction and Ligands Used



lectivity compared to the complex of nonsubstituted BINOL ligand (96% vs 90% ee, respectively, Table 1). In all the cases, we observed a very good yield (>90%) of the model reaction. The molar ratio of BINOL/Ti(IV) (1:1 or 2:1) was of no significance for this reaction, but the complexes L_2/Ti revealed a slightly better ee, were more active,[25] and also had a positive nonlinear effect (Figure 1).

Table 1. Screening of the BINOL/Ti Complexes in the Reaction of **1a** with **2**[a]

entry	catalyst		yield (%)[b]	ee (%)[c]
1	**L1**/Ti(OPr^i)$_4$	1: 1	93	89
2	**L1**/Ti(OPr^i)$_4$	2: 1	94	90
3	**L2**/Ti(OPr^i)$_4$	1: 1	92	95
4[d]	**L2**/Ti(OPr^i)$_4$	2: 1	94	96

[a] The reactions were carried out using of 2 mol % of catalyst, 1.5 mmol of *n*-butyl glyoxylate (**2**) in 2 mL of toluene, and 1.0 mmol of silvan (**1a**), at 0 °C (2 h). [b] Isolated yield. [c] Enantiomeric excess determined by GC and HPLC using chiral columns. [d] For reaction carried out in Et_2O and CH_2Cl_2, yields and enantioselectivities were 98% and 92% ee and 94% and 93% ee, respectively.

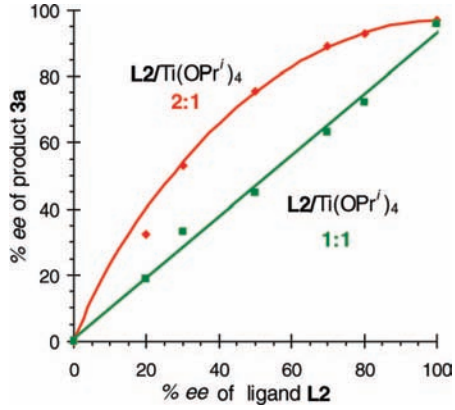


Figure 1. Effect of optical purity of **L2** on the reaction ee.

At the next stage of our studies, we decided to use the 6,6′-dibromo-BINOL/Ti catalyst of 2:1 stoichiometry. Among the tested solvents (toluene, CH_2Cl_2, Et_2O), toluene gave the best results, even without drying. As shown in Table 2, loading of the catalyst (0.5−5 mol %, entries 1−3), temperature (in the range of −20 to +20 °C, entries 1, 4, and 5), and reagent concentrations (0.5 and 0.25 mol/L, entries 1 and 6) had rather negligible effect on the ee of this model reaction. The yield was lower only in the case when furan was used in excess (entry 7, yield calculated with respect to glyoxylate). We also investigated other alkyl glyoxylates in this reaction. For *t*-butyl and *iso*-propyl glyoxylates, the yields and enantioselectivity were lower compared to *n*-butyl, and commercially available ethyl glyoxylate gave slightly lower enantioselectivity.[31] What is important is that this reaction needs not to use freshly distilled *n*-butyl glyoxylate and dry toluene to obtain satisfactory ee.

Having established the optimized conditions for asymmetric reactions of 2-methylfuran (**1a**) with **2**, we investigated the F−C reaction with other furan derivatives. As shown in Table 3, this reaction works well for a broad range of substituted furans usually affording very good yield and enantioselectivity (usually >90% ee). 2-Alkyl-substituted furans gave very good yield and enantioselectivity with 2 mol % of the catalyst (**L2**)$_2$/Ti(OPr^i)$_4$ at 0 °C in 2−3 h (Table 3, entries 1 and 3−6, conditions A). Only in the case of 2-*t*-butylfuran, the results were slightly worse (entry 4). Use of the less reactive nonsubstituted furan (**1b**, entry 2, conditions B) resulted in a significant drop in yield, although the enantioselectivity was still high.

Table 2. Optimization of the Model Reaction of **1a** with **2**[a]

entry	mol % of the cat. (**L2**)$_2$/Ti(OPr^i)$_4$	temp (°C)	yield (%)[b]	ee (%)[c]
1	2	0	94	96
2	5	0	96	96.5
3	0.5	0	89	96
4	2	−20	81	97
5	2	20	95	93
6[d]	2	0	90	97
7[e]	2	0	71	96

[a] The reactions were carried out with 1 mmol of silvan (**1a**) and 1.5 mmol of *n*-butyl glyoxylate (**2**) in 2 mL of toluene. [b] Isolated yield. [c] ee determined by GC and HPLC. [d] Reaction in 4 mL of toluene. [e] Excess of silvan was used (1.5 equiv), yield with respect to glyoxylate.

We have also studied the reaction of **2** with benzyl furfuryl ether (**1g**, entry 7), that was originally used by Achmatowicz in the total synthesis of racemic uloses.[10a] This reaction, due to lower reactivity of furan **1g** compared to 2-alkylfurans, requires 5 mol % of the catalyst, higher temperature, and longer reaction time (conditions B). Under the modified conditions, we obtained the product **3g** in 85% yield and 95% ee (Table 3, entry 7).

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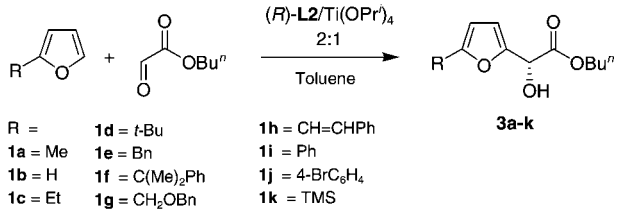
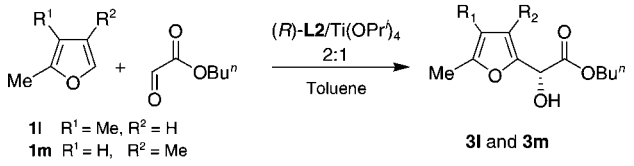
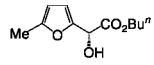
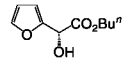
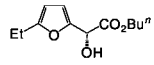
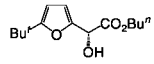
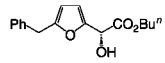
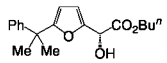
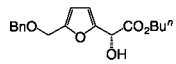
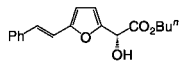
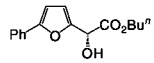
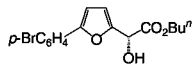
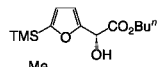
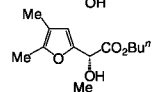
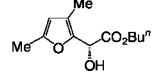
(31) Finally, we decided to use *n*-butyl glyoxylate because of difficulties with reproducibility of results experienced for ethyl glyoxylate, as well as difficulties with purification of ethyl esters by chromatography on silica, because of similarity of their Rf values to that of 6,6′-Br_2-BINOL.

Table 3. Scope of Furans in the Friedel−Crafts Reaction with **2** Catalyzed by ((*R*)-6,6′-Br_2-BINOL)$_2$/Ti(OPr^i)$_4$[a]





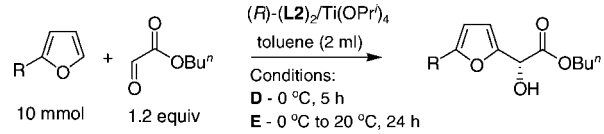
entry	furan	conditions[b]	product no.	product structure	yield (%)[c]	ee (%)[d]
1	**1a**	A	**3a**		92	97 (*R*)
2	**1b**	B	**3b**		45	91 (*R*)
3	**1c**	A	**3c**		98	94
4	**1d**	A	**3d**		80	90
5	**1e**	A	**3e**		90	95
6	**1f**	A	**3f**		89	94
7	**1g**	B	**3g**		85	95
8	**1h**	C	**3h**		98	94
9	**1i**	C	**3i**		90	90
10	**1j**	C	**3j**		96	88
11	**1k**	B	**3k**		76	89
12	**1l**	A	**3l**		77	96 (*R*)
13	**1m**	A	**3m**		95	96

[a] The reactions were carried out using 2 mol % or 5 mol % of the catalyst (**L2**)$_2$/Ti(OPr^i)$_4$, 1.5 mmol of *n*-butyl glyoxylate (**2**) in 2.0 or 4.0 mL of toluene, and 1.0 mmol of furan **1a**, **1c**−**1m** (**1b** was used in excess). [b] Conditions A: 2 mol % of the catalyst, 4.0 mL of toluene, 0 °C, 2−3 h; B: 5 mol % of the catalyst, 2.0 mL of toluene, 0 to 20 °C, 20 h; C: 5 mol % of the catalyst, 2.0 mL of toluene, 0 °C, 4 h. [c] Isolated yield. [d] Enantiomeric excess determined by GC and HPLC using chiral columns.

This reaction is not limited to 2-alkyl-substituted furans only. It works well also with vinyl, aryl, and silicon 2-substituted furans (entries 8−11). A very high yield and enantioselectivity was obtained with 2-styrylfuran (**1h**, entry 8, conditions C). Reactions with 2-arylfurans **1j** and **1k** (entries 9 and 10, conditions C) and 2-(trimethylsilyl)furan (entry 11, conditions B) gave a slightly lower enantioselectivity of about 90%. At least we demonstrated that this reaction can be successfully carried out using also the disubstituted, e.g., 2,3- and 2,4-dimethylfurans, to give 96% ee (entries 12 and 13, respectively).

We also demonstrated that this methodology worked effectively for the reactions on a multigram scale with low loading of the catalyst (**L2**)$_2$/Ti (0.1−0.5 mol %) and higher concentration of reagents, affording a very good yield and enantioselectivity over 91% with 2-methylfuran (Scheme 3).

Scheme 3. Scaled-Up Synthesis of 2-Furanyl-hydroxyacetates



R =	cat.		product	yield	ee
1a = Me	0.5 mol %	**D**	**3a**	95 %	95 %
	0.1 mol %	**E**		92 %	92 %
1f = CMe_2Ph	0.5 mol %	**D**	**3f**	95 %	93 %
1g = CH_2OBn	0.5 mol %	**E**	**3g**	90 %	91 %

A high yield and good ee was obtained also for furan **1f** (10 mmol scale, 0.5 mol % of the catalyst) and even for less reactive 2-benzyloxymethylfuran (**1g**).

Out of thirteen products, **3a**−**m**, three compounds (**3a**, **3b**, **3l**) have been subjected to determination of the absolute configuration by chemical correlations.[6b,7b,18] In all these cases, the products having (*R*) configuration were obtained from the (*R*)-6,6′-Br_2-BINOL/Ti complex. Such a direction of induction is in accordance with the literature data concerning the other F−C reactions[28,29] as well as the additions and cycloadditions to glyoxylates catalyzed by BINOL−Ti complexes.[24,25,32]

In summary, we have developed an efficient and easy method for the enantioselective synthesis of the very interesting building blocks chiral variously 5-substituted 2-furanyl-hydroxyacetates in good yield and high optical purity (ee usually >90%, up to 97%). The reaction is clearly and reproducibly catalyzed by the (6,6′-Br_2−BINOL)$_2$/Ti(IV) complex readily prepared from the commercially available reagents with no need of using dry toluene and inert atmosphere. According to our knowledge, this is the first example of efficient and highly enantioselective reaction of furans with glyoxylates.

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Supporting Information Available: Experimental procedures and analytical data for all the F−C products (**3a**−**m**) with reprints of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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