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Highly Enantioselective Friedel−Crafts Reaction of Thiophenes with Glyoxylates: Formal Synthesis of Duloxetine

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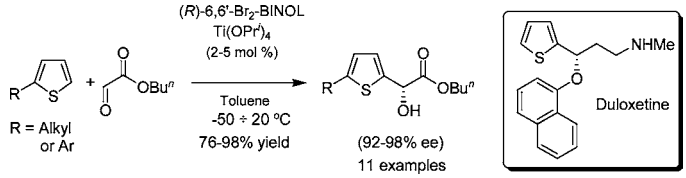
ABSTRACT



An efficient Friedel−Crafts reaction of a series of 2-substituted thiophenes with alkyl glyoxylates has been developed using a catalytic amount of an easy accessible 6,6′-dibromo-BINOL/Ti(IV) complex. A variety of hydroxy(thiophene-2-yl)acetates can be synthesized in high enantioselectivites (92−98% ee) and good yields. This is the first report on the efficient asymmetric F−C reaction of thiophenes with alkyl glyoxylates. Starting from simple thiophene and *n*-butyl glyoxylate, we demonstrated the formal synthesis of duloxetine.

The thiophene ring can be recognized in various biologically active compounds with applications in medicine[1] or agrochemistry,[2] which often reveal higher activity compared to analogous phenyl-type substituents.[3] Structures containing thiophenes are also useful in the synthesis of new materials[4] and catalysts.[5] Quite stabile S−metal bonds create the possibility of using thiophene derivatives as ligands for catalysis.[5] Moreover, oligothiophenes are interesting materials in organic electronics[6] and in the preparation of fluorescent biosensors.[7]

We focused our attention on the enantioselective synthesis of chiral derivatives of 2-thienylcarbinols directly from simple thiophenes and reactive carbonyl compounds, e.g., glyoxylates. The Friedel−Crafts (F−C) hydroxyalkylation reaction of this type seems to offer a very attractive, direct, and atom-economic approach to the synthesis of hydroxy-

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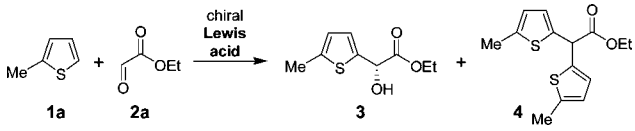
(thiophene-2-yl)acetates. However, to the best of our knowledge, until now there has been no report on successful catalytic enantioselective F−C reaction of thiophenes with aldehydes and ketones.[8] One of the difficulties could be the reactivity of thiophene toward electrophiles, which is lower than for pyrrole, indole, and furan.[9] The literature describes examples of efficient enantioselective reactions of reactive carbonyl compounds (e.g., glyoxylates) with other activated arenes and heteroarenes (e.g., anilines[10] and indoles[11]). Recently, we demonstrated a highly enantioselective synthesis of furan-2-yl-hydroxyacetates from furans and glyoxylates.[12]

Concerning applications of thiophenes in asymmetric catalytic F−C reactions, Jørgensen and co-workers reported an enantioselective reaction of trifluoropyruvate with 2-methylthiophene catalyzed by *t*-Bu-BOX−Cu(II) complexes with 79% ee and only 16% yield.[13] Much better results were obtained in the enantioselective reaction of activated thiophenes with α-imino esters.[14]

The catalytic reaction of thiophenes and other arenes and heteroarenes with glyoxylates in a racemic version was investigated by Wang.[15] Using $Yb(OTf)_3$ as a catalyst in the reaction of 2-methylthiophene (**1a**) and ethyl glyoxylate (**2a**), instead of compound **3** they isolated product **4** containing two thiophene rings in good yield (Scheme 1, the model

Scheme 1. Model Friedel−Crafts Reaction



reaction in our studies); however, with other arenes the desired α-hydroxy ester was received. Results obtained with 2-methylthiophene suggest that control of chemoselectivity in this reaction is not trivial.

Herein we describe the first highly enantioselective Friedel−Crafts reaction of variously substituted thiophenes **1a**−**k** with ethyl or *n*-butyl gloxylates (**2a** and **2b**) yielding hydroxy(thiophene-2-yl)acetates. Initially, the reaction between commercially available ethyl gloxylate (**2a**) and 2-methylthiophene (**1a**) (Scheme 1) was studied in the presence of well-known types of chiral Lewis acids, e.g., (*R*,*R*)-(Salen)$CrBF_4$ (**5**), (*R*)-Ph-BOX/$Cu(OTf)_2$ (**6**), and BINOL/$Ti(OPr^i)_4$ (**7**) (Figure 1). With salen−chromium and

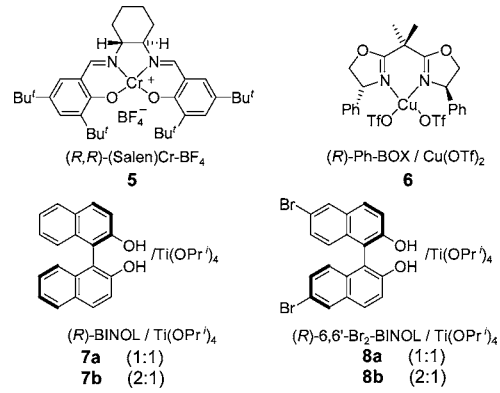


Figure 1. Chiral Lewis acid catalysts used.

bisoxazoline−copper complexes, we observed low ee of product **3** and also formation of byproduct **4** (Table 1).

Table 1. Screening of Chiral Lewis Acids in the Reaction of **1a** with **2**[a]

entry	catalyst	yield of **3**[e] (%)	ee of **3**[f] (%)	yield of **4**[e] (%)
1[b]	**5**	54	26	12
2[b,c]	**6**	44	28	14
3	**7a**	68	81	*g*
4	**7b**	83	82	*g*
5	**8a**	89	84	*g*
6	**8b**	90	84	*g*
7[d]	**8b**	90	90	*g*

[a] The reactions were carried out using 2 mol % of catalyst and 1.5 mmol of ethyl glyoxylate (**2a**) in 2 mL of toluene and 1.0 mmol of 2-methylthiophene (**1a**) at 0 °C (3 h). [b] 5 mol % of catalyst, from 0 to 20 °C (5 days). [c] 2 mL of dry THF. [d] Reaction with 1.5 mmol of *n*-butyl glyoxylate (**2b**). [e] Isolated yield. [f] Enantiomeric excess determined by HPLC using chiral columns. [g] Product was not observed on TLC.

BINOL−Ti complex, generated in situ from BINOL ligand and $Ti(OPr^i)_4$, proved sufficiently active to catalyze this reaction with good yield and selectively to product **3** and also higher and promising enantioselectivity (82% ee). BINOL−titanium complexes were introduced to asymmetric catalysis by Mikami[16] and Keck[17] and used in F−C type reactions for the first time by Mikami.[18] We also successfully applied this catalyst for F−C reactions of furans with glyoxylates.[12]

To compare the relative reactivity of furans and thiophenes in the investigated reaction we mixed 2-methylthiophene

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(**1a**), 2-methylfuran, and ethyl glyoxylate in a ratio of 1:1:1 in the presence of BINOL−Ti catalyst. This competitive experiment showed that thiophene is significantly less reactive, and an almost exclusively furan-containing product was formed (25:1 product ratio); however, in the absence of furan we were able to obtain product **3** with good yield.

Among the BINOL−titanium catalysts, the complex containing 6,6′-Br_2BINOL ligand (catalyst **8**) gave slightly better results in terms of yield and enantioselectivity compared to nonsubstituted BINOL. The molar ratio of BINOL/Ti (1:1 or 2:1) has practically no influence on this reaction; however, the complexes **7b** and **8b** (2:1) are usually slightly more active and enantioselective. At the next stage of our research, we decided to use the 6,6′-dibromo-BINOL/Ti catalyst of 2:1 stoichiometry. Replacing commercially available ethyl glyoxylate (84% ee, Table 1, entry 6) with *n*-butyl glyoxylate resulted in an increase of enantiomeric excess to 90% (entry 7).[19]

Optimization studies with titanium complex **8b** revealed that toluene gave better results than CH_2Cl_2 and Et_2O. 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, 6, and 7), and reagent concentration (0.5−1 mol/L, entries 1 and 4) had a rather negligible effect on the ee of this model reaction. The yield was lower only in the case when thiophene was used in excess (entry 5, yield calculated with respect to glyoxylate) or when the reaction was carried out at very low temperature (entry 9). In conclusion, 2 mol % of catalyst at −50 °C seems to be the optimal condition for the model reaction and provides the product with 94% ee and good yield. Importantly, this reaction does not require the use of dried toluene to obtain high ee.

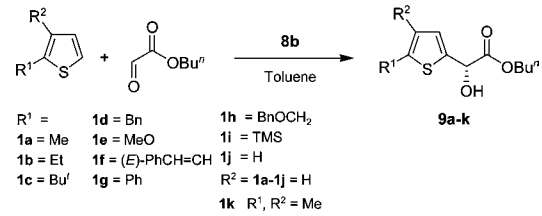
Table 2. Optimization of the Model Reaction of **1a** with **2b**[a]

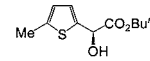
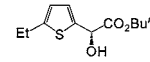
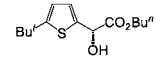
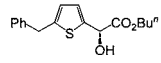
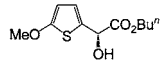
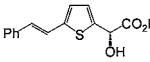
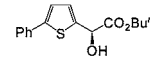
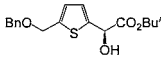
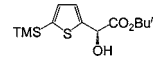
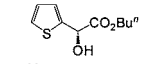
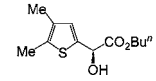
entry[a]	**8b** (mol %)	*T* (°C)	toluene (mL)	yield[b] (%)	ee[c] (%)
1	2	0	2	90	90
2	5	0	5	91	91
3	0.5	0	0.5	81	88
4	2	0	1	97	90
5[d]	2	0	2	70	90
6	2	20	2	87	85
7	2	−20	2	75	92
8[e]	2	−50	1	78	94
9[e]	2	−60	1	37	93

[a] The reactions were carried out with 1 mmol of 2-methylthiophene (**1a**) and 1.5 mmol of *n*-butyl glyoxylate (**2b**) for 3 h. [b] Isolated yield. [c] ee determined by HPLC. [d] An excess of 2-methylthiophene was used (1.5 equiv); yield with respect to glyoxylate. [e] The reactions was carried out for 7 h.

Having optimized conditions for asymmetric reactions of 2-methylthiophene with **2b**, we investigated the scope of thiophenes. As shown in Table 3, this reaction works well for a broad range of 2-substituted thiophenes, usually affording very good yield and enantioselectivity (92−98% ee).

Table 3. Scope of Thiophenes in Friedel−Crafts Reaction with **2b** Catalyzed by **8b**[a]



entry	thiophene	conditions[b]	product no	product structure	yield (%)[c]	ee (%)[d]
1	**1a**	A	**9a**		78	94
2	**1b**	A	**9b**		80	95
3	**1c**	A	**9c**		80	98
4	**1d**	A	**9d**		76	96
5	**1e**	A	**9e**		92	94
6	**1f**	B	**9f**		97	94
7	**1g**	B	**9g**		85	94
8	**1h**	C	**9h**		85	94
9	**1i**	C	**9i**		65	92
10	**1j**	C	**9j**		40	92
11	**1k**	A	**9k**		83	93

[a] The reactions were carried out using 2 mol % or 5 mol % of the catalyst **8b** and 1.5 mmol of *n*-butyl glyoxylate (**2b**) in 1.0 or 2.0 mL of toluene and 1.0 mmol of thiophene (**1a**−**1k**). [b] Conditions: (A) 2 mol % of the catalyst, 1.0 mL of toluene, −50 °C, 7 h; (B) 5 mol % of the catalyst, 2.0 mL of toluene, 0 °C, 4 h; (C) 5 mol % of the catalyst, 2.0 mL of toluene, 0−20 °C, 24 h. [c] Isolated yield. [d] Enantiomeric excess determined by HPLC using chiral columns.

Optimized conditions for the model reaction (2 mol % of catalyst **8b** at −50 °C for 7 h; conditions A) work very well with other thiophenes substituted with alkyl groups at position 2 (e.g., Et, *t*-Bu, Bn, entries 2−4). Also, the reaction of highly activated 2-methoxythiophene with **2b** at −50 °C gives product with very high ee and yield (entry 5).

Higher loading of catalyst (5 mol %) and temperature 0 °C was applied for thiophenes substituted with aryl and vinyl groups (conditions B, entries 6 and 7). Reactions with less reactive thiophenes having protected hydroxymethyl and trimethylsilyl groups or nonsubstituted thiophene (entries 8−10) require higher temperature and prolonged reaction time (conditions C, 20 °C, 24 h). However, use of nonsub-

(19) Other alkyl glyoxylates were also investigated in this reaction; for *tert*-butyl and isopropyl glyoxylates, the yields and enantioselectivity were lower compared to *n*-butyl glyoxylate.

stituted thiophene resulted in a significant drop in yield, although the enantioselectivity was still high (entry 10). Reaction is also possible with disubstituted thiophenes. Very high enantioselectivity and yield were obtained using 2,3-dimethylthiophene (entry 11). In the case of 2,5-dimethylthiophene, product substituted in position 3 was formed, albeit with low enantioselectivity (35% ee). In conclusion, this method works very well for 2-substituted thiophenes with alkyl, vinyl, aryl, and other activating groups.

We also demonstrate that this methodology works effectively in multigram scale for thiophenes **1c**, **1f**, **1h** and low loading of catalyst **8b** (1−2 mol %) affording products with very good yield and enantioselectivity (Table 4).

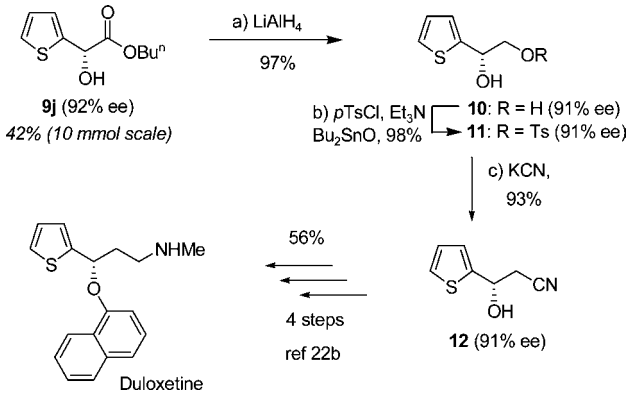
Table 4. Scaled-Up Synthesis of Hydroxy(thiophene-2-yl)acetates

product	conditions[a]	yield (%)	ee (%)
9c	1 mol % of **8b**; −50 °C for 12 h	73; 1.97 g	97
9f	2 mol % of **8b**; 0 °C for 24 h	98; 3.10 g	93
9h	2 mol % of **8b**; 0 → 20 °C for 24 h	78; 2.61 g	93

[a] Catalyst **8b** and 1.25 equiv of *n*-butyl glyoxylate (**2b**); a higher concentration of reagents was used.

We have also demonstrated application of the product **9j** in the formal synthesis of duloxetine (Scheme 2),[20] a

Scheme 2. Formal Synthesis of Duloxetine



serotonin−norepinephrine reuptake inhibitor of wide pharmacology utility.[21] Our approach is an alternative to the other duloxetine synthesis described in the literature.[22]

We scaled up the reaction of simple thiophene with *n*-butyl glyoxylate and 1 mol % of catalyst **8b**. The reaction provides product **9j** with moderate yield (42%) and 92% enantioselectivity. The F−C product was reduced to the diol **10**, and the primary hydroxy group was protected with tosyl group (**11**) which was subsequently substituted with cyanide. The nitrile **12** was obtained in three steps from F−C product **9j** with 88% yield. The nitrile is known in the literature and was applied in a four-step synthesis of duloxetine in 56% yield.[22b] Using our methodology, we can easily synthesize new analogues of duloxetine with a modified thienyl ring.

Absolute configuration was determined for 2 of 11 products: for **3** directly using X-ray crystallographic analysis (Figure 2) and for **9j** based on chemical correlation to (*S*)-(−)-nitrile **12**. Hydroxy(thiophene-2-yl)acetates having (*S*) configuration were obtained from the (*R*)-6,6′-Br_2-BINOL/Ti complex. Such a direction of induction is in accordance with the data in the literature concerning other F−C reactions[10b] catalyzed by BINOL−Ti complexes.

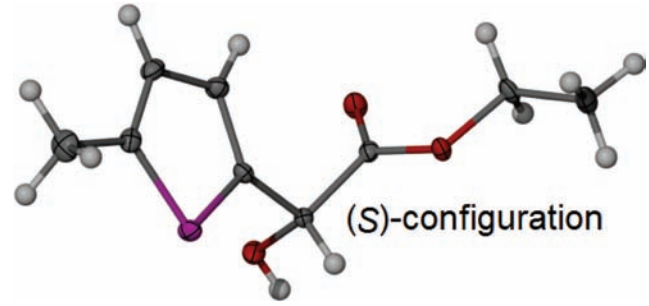


Figure 2. X-ray crystal structure of compound (*S*)-**3**: assignment of absolute configuration.

In summary, we have developed an efficient method for the enantioselective synthesis of chiral variously 5-substituted thiophene-2-yl α-hydroxy esters from thiophenes and *n*-butyl glyoxylate in good yield and high optical purity (92−98% ee), utilizing readily available (6,6′-Br_2-BINOL)$_2$/Ti(IV) complex as a catalyst. To our knowledge, this is the first example of the highly enantioselective reaction of thiophenes with aldehydes, namely glyoxylates. Moreover, the product of the reaction between thiophene and *n*-butyl glyoxylate was applied to the formal synthesis of duloxetine.

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Supporting Information Available: Experimental procedures and analytical data for all F−C products (**3**, **9a**−**k**) with copies of NMR spectra and CIF file for product (*S*)-**3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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