ORGANIC LETTERS

2011
Vol. 13, No. 22
5944–5947

Enantioselective Friedel–Crafts Reaction of Acylpyrroles with Glyoxylates Catalyzed by BINOL–Ti(IV) Complexes

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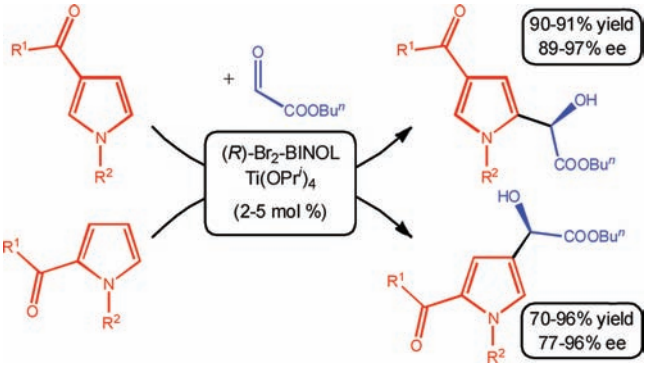
Received August 18, 2011

ABSTRACT



We report the first efficient enantioselective Friedel–Crafts hydroxyalkylation of pyrroles having one electron-withdrawing group at the α, β or *N*-positions with alkyl glyoxylates catalyzed by readily available chiral BINOL–Ti(IV) complexes (1–5 mol %). The reaction regioselectively led to the desired pyrrole-hydroxyacetic acid derivatives with good yields (70–96%) and enantiomeric excesses up to 96%, and is applicable in multigram scale with low loading of the catalyst (1 mol %).

Chiral pyrrole derivatives are important compounds for the synthesis of many interesting biologically active molecules, chiral catalysts, and receptors.[1] Of special interest are derivatives with a sterogenic center in the α-position to the pyrrole ring. Acylpyrrole systems, on the other hand, are abundant in natural products[2] and other biologically active molecules, including synthetic drugs, e.g., ketorolac, tolmetin, atorvastatin, indanomycin, calcimycin, and pyrrole C-nucleosides.[3] The Friedel–Crafts (F–C) reaction is one of the most useful and straightforward approaches to aromatic system synthesis with a stereogenic carbon center in the benzylic position. In the literature there are many examples of enatioselective F–C reactions of aromatic and heteroaromatic compounds with a wide range of electrophiles in the presence of various chiral catalysts.[4] The literature describes enantioselective F–C reactions of

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10.1021/ol202244u
Published on Web 10/19/2011

pyrroles with α,β-unsaturated carbonyl compounds,[5] nitroolefins,[6] imines,[7] and ketones,[8] but there are no examples of analogous reactions with aldehydes. On the other hand, application of acylpyrroles in asymmetric F−C reactions is very limited.[7c,8b]

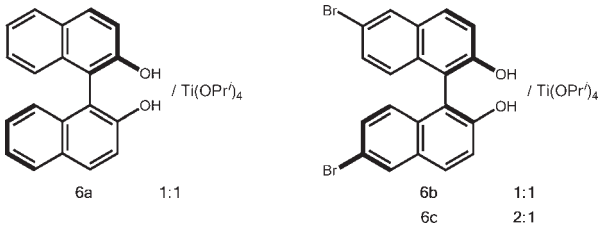


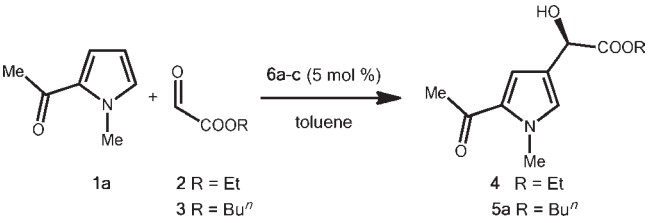
Figure 1. BINOL−Ti catalysts **6a**−**c**.

Herein we describe a highly enantioselective Friedel−Crafts reaction of acylpyrroles with alkyl glyoxylates catalyzed by BINOL−Ti(IV) complexes (Figure 1). This reaction allows for the synthesis of chiral pyrrolyl-hydroxyacetates, a structural motif that can be found in various biologically active molecules.[9] To date, compounds of this type have been synthesized using different approaches.[10,9a]

In our investigation we focused on enantioselective F−C reactions of pyrroles having one electron-withdrawing group (EWG) at the α, β or *N*-positions with activated aldehydes, e.g. alkyl glyoxylates. Pyrroles with other types of substituents are more nucleophilic and usually easily form racemic products with alkyl glyoxylates and arylglyoxals without catalysts.[11]

Recently we reported a highly enantioselective F−C reaction of furans and thiophenes with alkyl glyoxylates catalyzed by the optically pure 6,6′-dibromo-BINOL−Ti(IV) complex as the most efficient catalyst.[12] An asymmetric F−C reaction of indoles with ethyl glyoxylate catalyzed by similar complexes was discovered by Xiao and coworkers.[13] In this case, the corresponding ethyl 3-indolyl-(hydroxy)acetates were formed in good yields and with high enantiomeric excess. Those results encouraged us to study the reaction of pyrroles with activated aldehydes.

Table 1. Optimization of the Model Reaction of **1a** with **2** and **3**[a]



entry	product	catalyst (5 mol %)	temp (°C)	yield (%)[b]	ee (%)[c]
1	**4**	**6a**	0	65	79
2	**4**	**6b**	0	64	91
3	**4**	**6c**	0	77	91
4	**5a**	**6c**	0	85	93
5	**5a**	**6c**	20	80	89
6	**5a**	**6c**	−40 to 0	90	93

[a] The reactions were carried out using 5 mol % of catalyst (**6a**−**c**), 1.5 mmol of alkyl glyoxylate (**2** or **3**) in 2 mL of toluene, and 1.0 mmol of 2-acetyl-1-methylpyrrole (**1a**), at appropriate temperature. [b] Isolated yield. [c] Enantiomeric excess determined by HPLC using chiral columns.

We initially investigated the reaction of commercially available 2-acetyl-1-methylpyrrole (**1a**) and ethyl glyoxylate (**2**) in the presence of BINOL−Ti(IV) complexes **6a**−**c** in toluene (Figure 1, Table 1). The catalyst **6b** derived from (*R*)-6,6′-dibromo-BINOL give higher enantioselectivity (91% *ee,* entry 2) than catalyst **6a** with unsubstituted (*R*)-BINOL (79% *ee,* entry 1). Adjusting the molar ratio of BINOL and Ti(OPr^i)$_4$ led to a slight improvement in yield, when a 2:1 complex (catalyst **6c**) was employed (entry 3). In further studies, we decided to use catalyst **6c**, also because of the positive nonlinear effect which was observed in our previous work.[12a] Changing ethyl glyoxylate (**2**) to the more stable *n*-butyl glyoxylate (**3**) brought a slight increase in the enantiomeric excess (93% ee) and yield (85%) of product **5a** (entries 4−6).

After establishing the optimal conditions for the model reaction we explored the scope and the generality of the F−C reaction with other acylpyrroles. The various 2-acyl-1-methylpyrroles **1b**−**g** were reacted with *n*-butyl glyoxylate (**3**) in the presence of 5 mol % of the (*R*)-6,6′-dibromo-BINOL/Ti(IV) complex (**6c**) in toluene (Table 2). In all the cases, the reaction provided regioselectively 2,4-substituted products **5b**−**g** with good yields (75−96%) and high enantiomeric excesses (89−96%). In most cases, the

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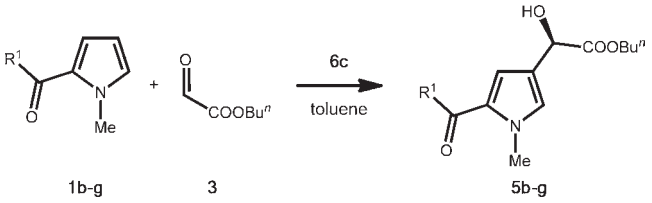
Table 2. Scope of the Friedel–Crafts Reaction of *N*-Me Pyrroles with Glyoxylate **3** Catalyzed by **6c**[a]



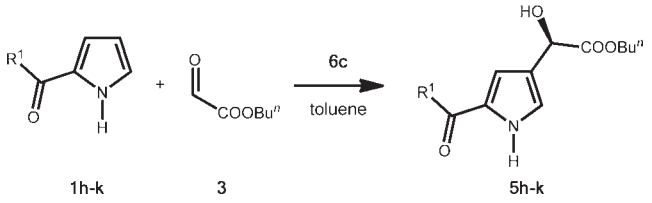
1b-g 3 5b-g

entry	R^1	substrate	product	mol % of cat. **6c**	yield (%)[b]	ee (%)[c]
1	Bu^t	**1b**	**5b**	5	89	96
2	Bn	**1c**	**5c**	5	85	93
3	Ph	**1d**	**5d**	5	75	96
4	m-$NO_2C_6H_4$	**1e**	**5e**	2	94	96
5	p-$NO_2C_6H_4$	**1f**	**5f**	2	96	96
6	MeO	**1g**	**5g**	5	90	89

[a] The reactions were carried out using 2 or 5 mol % of catalyst **6c**, 1.5 mmol of *n*-butyl glyoxylate (**3**) in 2 mL of toluene, and 1.0 mmol of 2-acyl-1-methylpyrrole (**1b**–**g**), at lowered temperature (from −40 to 0 °C). [b] Isolated yield. [c] Enantiomeric excess determined by HPLC using chiral columns.

regioisomeric 2,5-substituted products were not observed. The reaction can be carried out with excellent yield and enantioselectivity also using a lower amount of catalyst (2 mol %) (see products **5e** and **5f**).

Table 3. Scope of the Friedel–Crafts Reaction of *N*-H Pyrroles with Glyoxylate **3** Catalyzed by **6c**[a]



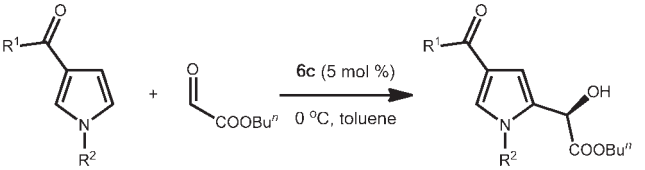
1h-k 3 5h-k

entry	R^1	substrate	product	**6c** (mol %)	time (h)	yield (%)[b]	ee (%)[c]
1	Me	**1h**	**5h**	5	10	71	81
2	Bu^t	**1i**	**5i**	5	5	80	95
3	Ph	**1j**	**5j**	5	10	70	77
4	MeO	**1k**	**5k**	2	5	82	94

[a] The reactions were carried out using 2 or 5 mol % of catalyst **6c**, 1.5 mmol of *n*-butyl glyoxylate (**3**) in 2 mL of toluene, and 1.0 mmol of 2-acylpyrrole (**1h**–**k**), at 0 °C. [b] Isolated yield. [c] Enantiomeric excess determined by HPLC using chiral columns.

It is also noteworthy that the F–C reactions carried out with N-unprotected acylpyrroles **1h**–**k** give the desired products **5h**–**k** (Table 3). Methyl group absence at the nitrogen does not have a negative influence on the yield (70–91%) and enantiomeric excesses (74–95%). Moreover, products containing unprotected pyrroles provide an opportunity for further functionalization on the nitrogen atom.[14]

Scheme 1. Friedel–Crafts Reaction of 3-Acylpyrroles (**1l**, **1m**) with Glyoxylate **3** Catalyzed by **6c**



1l R^1 = Bu^t, R^2 = Me
1m R^1 = Me, R^2 = H

5l 90% yield, 89% ee (3 h)
5m 91% yield, 97% ee (5 h)

We also examined two examples of the F–C reaction of 3-acylpyrroles (**1l**, **1m**) with *n*-butyl glyoxylate (Scheme 1). The reaction provides products with high yields and enantioselectivity but different regioselectivity, which depends on the position of the EWG in the pyrrole ring. In general, pyrroles bearing EWGs (e.g., Ac, ArCO, MeO_2C) in position 2 lead to electrophilic substitution in position 4 (Tables 2 and 3), whereas an EWG in position 3 directs glyoxylate on position 5 (Scheme 1). The observed regioselectivity is in agreement with the literature,[15] and the structures of products were confirmed by NOE experiments.[16]

Use of more activated pyrroles (without an EWG, e.g., 1-methylpyrrole or 2-styryl-1-methylpyrrole) and our reaction conditions give practically racemic products. This problem could be circumvented by introducing a protecting EWG on the nitrogen atom (e.g., Boc or Cbz). The Friedel–Crafts reaction of 1-Boc-pyrrole (**1n**) and 1-Cbz-pyrrole (**1o**) with *n*-butyl glyoxylate (**3**) give desired chiral products (respectively **5n** and **5o**, Scheme 2), slightly contaminated with a difficult to separate byproduct.[17]

Another applicable substrate for this reaction is 1-Boc-2,5-dimethylpyrrole (**1p**), which with *n*-butyl glyoxylate (**3**) gives only 3-substituted product **5p** with high yield (91%) and acceptable enantiomeric excesses (75% ee, Figure 2). Pyrrole derivatives containing two electron-withdrawing groups (e.g., *N*-Boc or *N*-Cbz 2-acetylpyrrole) are not reactive enough in this reaction.

With a practical procedure in hand for synthesis of pyrrolyl-hydroxy acetates **5**, we turned our attention to scale-up (Table 4). A few products were prepared on the

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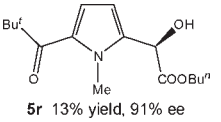
(16) For details see Supporting Information.

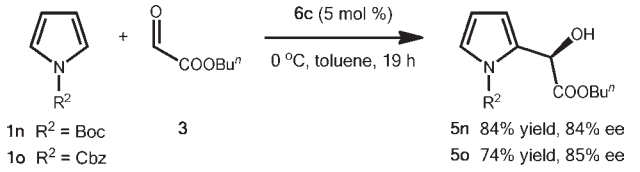
(17) We suppose that corresponding regioisomers substituted on the 3-position were obtained as byproducts.

(18) Reaction of 2-pivaloyl-1-methylpyrrole (**1b**) with *n*-butyl glyoxylate (**3**) provides two isomers, a mainly obtained product substituted on position four (**5b**) on the pyrrole ring and a byproduct **5r** substituted on position five.



5r 13% yield, 91% ee

Scheme 2. Friedel–Crafts Reaction of *N*-Boc and *N*-Cbz Pyrroles with Glyoxylate **3** Catalyzed by **6c**



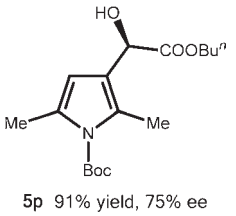


Figure 2. Product of reaction of 1-Boc-2,5-dimethylpyrrole (**1p**) with glyoxylate **3**.

10.0 mmol scale, using a low loading of the catalyst **6c** (1 mol %) and higher concentration of reagents (2.5 M). The results are comparable to 1.0 mmol scale reactions in terms of yield and enantioselectivity.

Table 4. Scaled-Up Synthesis of Pyrrolyl-hydroxy Acetates[a]

entry	substrate	product	mol % of cat. **6c**	yield (%)[b]	ee (%)[c]
1	**1b**	**5b**	1	78	96[18]
2	**1f**	**5f**	1	90	96
3	**1h**	**5h**	1	72	79

[a] The reactions were carried out using 1 mol % of catalyst **6c**, 12.0 mmol of *n*-butyl glyoxylate (**3**) in 4 mL of toluene, and 10.0 mmol of pyrrole (**1b**, **1f**, **1h**), at 0 °C. [b] Isolated yield. [c] Enantiomeric excess determined by HPLC using chiral columns.

In summary, we have demonstrated the first efficient regioselective and highly enantioselective Friedel–Crafts reaction of pyrroles with alkyl glyoxylates catalyzed by readily available chiral BINOL–Ti(IV) complexes. Among various tested substrates, pyrroles having one electron-withdrawing group at α, β or *N*-positions were the best substrates for this reaction. The products of this reaction provide easy access to important synthons in chemical synthesis which are commonly found in biologically active molecules, chiral catalysts, and receptors.

Supporting Information Available. Experimental procedures and analytical data for all the F–C products (**4**, **5a**–**r**) with reprints of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.