ORGANIC LETTERS

2009
Vol. 11, No. 2
441−444

Enantioselective Zirconium-Catalyzed Friedel−Crafts Alkylation of Pyrrole with Trifluoromethyl Ketones

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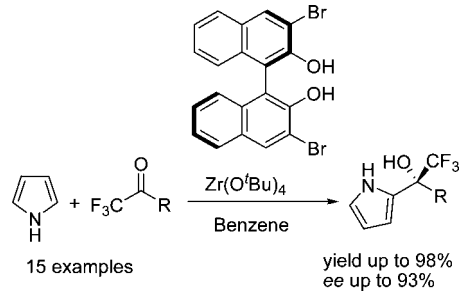
Received October 30, 2008

ABSTRACT



The first catalytic enantioselective Friedel−Crafts alkylation of pyrrole with 2,2,2-trifluoroacetophenones to give pyrroles with a trifluoromethyl-substituted tertiary alcohol moiety bearing a quaternary stereogenic center is described. The reaction is achieved in the presence of a 3,3′-dibromo-BINOL-Zr(IV) complex to give the expected products with high yields (up to 98%) and good enantioselectivities (up to 93% ee). The absolute stereochemistry of the products has been determined by chemical correlation.

Recently, trifluoromethylated compounds have received considerable attention, and they have diverse applications in the areas of materials science, agrochemistry and biomedical chemistry due to their unique chemical, physical, and biological properties.[1] On the other hand, the catalytic enantioselective construction of stereogenic tetrasubstituted carbon centers is a very challenging goal and a matter of current interest in organic chemistry.[2] The emergence of drugs such as Efavirenz (anti-HIV)[3] or CJ-17,493 (neurokinin 1 receptor antagonist),[4] two chiral α-trifluoromethyl tertiary alcohols in which the CF_3 moiety is located at a stereogenic tetrasubstituted carbon atom, has stimulated investigation in this area. In this context, two general strategies for the synthesis of this type of α-trifluoromethyl tertiary alcohol can be used. The first one is the trifluoromethylation of carbonyl compounds.[5] However, enantioselective trifluo-

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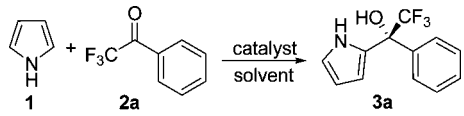
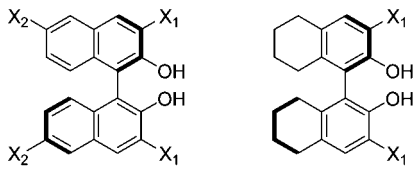
10.1021/ol802509m CCC: $40.75
Published on Web 12/10/2008

Scheme 1. Enantioselective F−C Reaction of Pyrrole with 2,2,2-Trifluoroacetophenone and BINOL-Type Ligands Used in This Study





(*R*)-**L1** $X_1 = X_2 = H$
(*R*)-**L2** $X_1 = H$, $X_2 = Br$
(*R*)-**L3** $X_1 = Br$, $X_2 = H$
(*R*)-**L6** $X_1 = 3,5\text{-}(CF_3)_2C_6H_3$-, $X_2 = H$

(*R*)-**L4** $X_1 = H$
(*R*)-**L5** $X_1 = Br$

romethylation is difficult to achieve, and high enantiomeric excesses are rarely reached except when the substrate is very hindered.[6] A second strategy would be the addition of carbon nucleophiles to trifluoromethyl ketones. However, the formation of quaternary carbons via the addition of carbon nucleophiles to ketones still constitutes a major challenge in synthetic chemistry.[2] So far, the use of trifluoromethyl ketones as acceptors in enantioselective addition reactions has been limited; the addition of organometallic zinc reagents[7] and arylboronic acids[8] and the Henry reaction being among the few reported examples.[9] To the best of our knowledge, no catalytic enantioselective Friedel−Crafts alkylation of aromatic substrates with trifluoromethyl ketones has been reported so far, with the exception of few examples with ethyl trifluoropyruvate.[10] Herein we report the first zirconium-catalyzed Friedel−Crafts alkylation of pyrrole with 2,2,2-trifluoroacetophenones reaching enantioselectivities up to 93% ee.

Table 1. Optimization of Enantioselective F−C Reaction of **1** and **2a** Catalyzed by Zr(IV)-BINOL Complexes[a]

entry	solvent	L	*t* (h)	yield (%)[b]	ee (%)[c]
1	CH_2Cl_2	**L1**	1.5	92	10
2	CH_2Cl_2	**L2**	1.5	98	8
3	CH_2Cl_2	**L3**	3.5	93	59
4	CH_2Cl_2	**L4**	1.2	90	9
5	CH_2Cl_2	**L5**	2.2	89	43
6	CH_2Cl_2	**L6**	17	64	48
7	THF	**L3**	20	42	66
8	dioxane	**L3**	22	34	66
9	toluene	**L3**	1.5	99	85
10	benzene	**L3**	1.5	97	90
11	F-C_6H_5	**L3**	1.2	98	80
12[d]	benzene	**L3**	3	91	74
13[e]	benzene	**L3**	1.5	96	78
14[f]	benzene	**L3**	2	96	76
15[g]	benzene	**L3**	1	87	78
16[h]	benzene	**L3**	2.5	87	78
17[i]	benzene	**L3**	1	99	78

[a] All reactions were performed with BINOL-type ligands **L** (0.05 mmol), $Zr(O^tBu)_4$ (0.05 mmol), pyrrole (1.25 mmol), and 2,2,2-trifluoroacetophenone (0.25 mmol) in 2 mL of solvent at room temperature unless otherwise stated. [b] Isolated yield of **3a** after flash chromatography. [c] Determined by HPLC using Chiralcel OD-H column. [d] Reaction temperature was 0 °C. [e] Reaction temperature was 50 °C. [f] Reaction was performed with ligand **L3** (10 mol %) and $Zr(O^tBu)_4$ (10 mol %). [g] Reaction was performed with ligand **L3** (10 mol %). [h] Reaction was performed with 3 equiv of pyrrole. [i] Reaction was performed with 10 equiv of pyrrole.

The reaction of pyrrole **1** with 2,2,2-trifluoroacetophenone **2a** was chosen to optimize the reaction conditions. BINOL-type ligands[11] and $Zr(O^tBu)_4$ in dichloromethane at room temperature[12] were evaluated as shown in the illustrated reaction (Scheme 1), and the results are summarized in Table 1. We used an excess of 5 equiv of pyrrole with respect to the trifluoromethyl ketone to avoid the formation of dialkylated products.[13] With ligands **L1**−**L5** the reaction was completed in 1.5−3.5 h, giving product **3a** with good yield (89−98%) but low/moderate enantioselectivity (8−59% ee) (entries 1−5), and the highly hindered 3,3′-disubstituted BINOL **L6** led to a lower yield (64% yield, 48% ee). Ligand **L3**, having two bromine atoms at the 3,3′ positions, led to the best result (93% yield, 59% ee) (entry 3). Next, we screened different solvents using ligand **L3**. Ether-type solvents (THF or dioxane) had a negative influence on the catalytic activity, although they slightly improved the enantioselectivity (entries 7 and 8). On the other hand, aromatic

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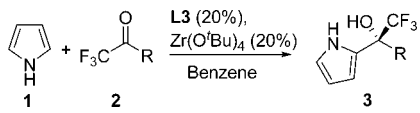
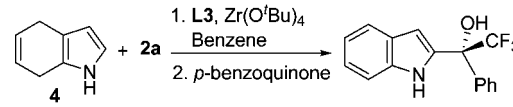
Scheme 2. Enantioselective F−C Reaction of Pyrrole with Trifluoromethyl Ketones Catalyzed by **L3**-Zr(O^{t}Bu)$_4$



Scheme 3. Reaction of 4,7-Dihydroindole (**4**) with **2a**



hydrocarbons (toluene, benzene, or fluorobenzene) improved both the catalytic activity and the enantioselectivity (entries 9−11). The best result was obtained using benzene as solvent (97% yield, 90% ee) (entry 10). Lowering the temperature to 0 °C or increasing the temperature to 50 °C had a negative effect on the enantioselectivity, resulting in 74% ee (entry 12) and 78% ee (entry 13), respectively. A catalyst loading reduction to 10 mol % also had a deleterious effect on the reaction, compound **3a** being obtained in 96% yield and 76% ee (entry 14). As conditions of choice, we used **L3**-Zr(O^{t}Bu)$_4$ in benzene, at room temperature, a catalyst loading of 20 mol %, and an excess of 5 equiv of pyrrole. An excess of 3 or 10 equiv of pyrrole had also a deleterious effect on the reaction (entries 16 and 17).

Table 2. Substrate Scope of Enantioselective F−C Reaction of Pyrrole (**1**) with Trifluoromethyl Ketones **2** Catalyzed by **L3**-Zr(OtBu)$_4$ According to Scheme 2[a]

entry	**2**	R	t (h)	**3**	yield (%)[b]	ee (%)[c]
1	**2a**	Ph	1.5	**3a**	97	90
2	**2b**	p-MeC$_6$H$_4$	1.5	**3b**	98	87
3	**2c**	p-EtC$_6$H$_4$	1	**3c**	95	87
4	**2d**	p-MeOC$_6$H$_4$	1	**3d**	99	86
5	**2e**	p-MeSC$_6$H$_4$	1	**3e**	84	93
6	**2f**	p-FC$_6$H$_4$	1.3	**3f**	98	85
7	**2g**	p-ClC$_6$H$_4$	1	**3g**	99	88
8	**2h**	p-BrC$_6$H$_4$	1	**3h**	99 (70)[d]	77 (97)[d]
9	**2i**	p-CNC$_6$H$_4$	2	**3i**	94 (73)[d]	72 (94)[d]
10	**2j**	m-MeC$_6$H$_4$	1	**3j**	93	85
11	**2k**	m-MeOC$_6$H$_4$	1	**3k**	96	86
12	**2l**	m-FC$_6$H$_4$	2	**3l**	94	80
13	**2m**	3,4-F$_2$C$_6$H$_3$	1	**3m**	96	63
14	**2n**	3,4-Cl$_2$C$_6$H$_3$	1	**3n**	96	68
15	**2p**	Et	1.2	**3p**	92	21

[a] All reactions were performed with ligand **L3** (0.05 mmol), Zr(O^{t}Bu)$_4$ (0.05 mmol), pyrrole (1.25 mmol), and trifluoromethyl ketone **2** (0.25 mmol) in benzene (2 mL) at room temperature unless otherwise stated. [b] Isolated yield after flash chromatography. [c] Determined by HPLC analysis using Chiralcel OD-H column. [d] In parenthesis, yield and ee of the product obtained from the mother liquors after crystallization of a nearly racemic mixture.

To explore the scope of the reaction various substituted 2,2,2-trifluoroacetophenones **2a**−**n** were reacted with pyrrole (**1**) (Scheme 2, Table 2). In all the cases, the reaction provided the expected products **3a**−**n** with good to high enantiomeric excesses (up to 93%). The presence of electron-donating groups (Me, Et, MeO, MeS) or electron-withdrawing-groups (F, Cl) in the aromatic ring had little influence on the enantioselectivity (entries 2−7). However, the presence of groups such as Br or CN (entries 8 and 9) lowered the enantiomeric excess of the products. Nevertheless these products could be obtained with high ee after recrystallization. The presence of a substituent on the *para* and *meta* positions of the aromatic ring in compound **2** did not affect either the reactivity or the enantioselectivity of the reaction (entries 2, 4, and 6 vs entries 10−12). However, the reaction with *o*-methyltrifluoroacetophenone took place with very low yield (5%), and the ee of the alkylation product dropped to 72%, indicating the existence of a steric effect caused by the *ortho* substituent. Finally, 2′,2′,2′,3,4-pentafluoroacetophenone (**2m**) and 3,4-dichloro-2′,2′,2′-trifluoroacetophenone (**2n**), with two additional substituents on the aromatic ring, could also serve as substrates in this reaction, giving the corresponding alkylated pyrroles in excellent yields and with good enantioselectivities (entries 13 and 14). Unfortunately, the reaction with aliphatic trifluoromethyl ketone **2p** (entry 15) took place with good yield (92%) but poor enantioselectivity (21% ee).

The effects of pyrrole substitution were also evaluated under the optimized conditions. *N*-Methylpyrrole led to mixtures of mono- and dialkylated products with poor enantioselectivity (ca. 50% ee), and 2-ethylpyrrole led to the C5 reaction product with excellent yield (95%) but very low enantioselectivity (22%). However, 4,7-dihydroindole (**4**), which can be considered as a disubstituted pyrrole, reacted with **2a** with excellent yield and good enantioselectivity to give the C2-alkylated indole **5** (Scheme 3) after oxidation with *p*-benzoquinone (92% overall yield for the two steps, 72% ee).[14]

The absolute stereochemistry of compound **3a** was determined by chemical transformation into the literature-known compound **6**.[15] This was accomplished by an oxidation procedure in analogy to the oxidative cleavage of furans.[13,16] Thus pyrrole **3a** was oxidized to the Mosher acid amide **6** upon treatment with $NaIO_4$ in the presence of $RuCl_3$ (Scheme 4). By comparison of the optical rotation, the absolute stereochemistry of the prepared compound **6**, and therefore of compound **3a**, was determined to be of the *R*-configuration, and for the rest of the products it was assigned on the assumption of a uniform reaction mechanism.

In summary, we have demonstrated the use of a zirconium(IV)/BINOL catalyst in a Friedel−Crafts reaction of unprotected pyrrole with a variety of differently substituted

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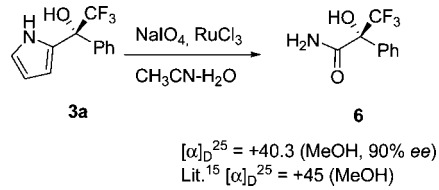
Scheme 4. Determination of Absolute Stereochemistry of Compound **3a**



$[\alpha]_D^{25}$ = +40.3 (MeOH, 90% *ee*)
Lit.[15] $[\alpha]_D^{25}$ = +45 (MeOH)

2,2,2-trifluoroacetophenones to give pyrroles with a trifluoromethyl substituted tertiary alcohol moiety. The reaction takes place with good enantioselectivities (up to 93%) and high isolated yields (up to 98%). Additional advantages are the use of ligands that are commercially available in both enantiomeric forms (hence providing access to both enantiomeric products) and a simple experimental procedure at room temperature. Further, the avoidance of using *N*-protecting groups in pyrrole alkylations also enhances the efficiency by which substituted pyrroles may be synthesized. We are currently directing our efforts toward enhancing the scope and enantioselectivity of this method, the elucidation of the mechanism, and the rationalization of the origin of the stereochemistry.

Acknowledgment. Financial support from the Ministerio de Educación y Ciencia and FEDER (Grant CTQ 2006-14199/BQU) is acknowledged. C.V. thanks the Generalitat Valenciana for a predoctoral grant.

Supporting Information Available: Experimental procedures, characterization data and copies of NMR spectra, and chiral analysis for compounds **3a**−**n**, **5**, and **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL802509M