Enantioselective Friedel–Crafts Reaction of Indoles with Trifluoroacetaldehyde Catalyzed by Cinchona Alkaloids

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ABSTRACT The first direct asymmetric synthetic preparation of trifluoro-1-(indol-3-yl)ethanols (TFIEs) is described by an enantioselective organocatalytic method from indoles and inexpensive trifluoroacetaldehyde methyl hemiacetal. The reaction is catalyzed by hydroquinine to produce TFIEs in an almost quantitative yield and with enantioselectivities up to 75% at room temperature. The enantioselectivity is strongly dependent on the concentration of substrates and catalyst due to the competitive noncatalyzed reaction. *Chirality 23:612–616, 2011.* © 2011 Wiley-Liss, Inc.

KEY WORDS: enantioselective; organocatalysis; Cinchona; indole; fluoral; chiral trifluoromethylated alcohols

INTRODUCTION

Organofluorine compounds, particularly trifluoromethylated derivatives, are highly important substances in organic and medicinal chemistry. As compared to their nonfluorinated analogues, the presence of the powerful electron-withdrawing substituent, its small size and lipophilic character generate significant changes in the chemistry and the biological effects of these compounds.[1,2] The increased lipophilicity of such molecules results in active agrochemical and pharmaceutical compounds with improved adsorption-distribution-metabolism-excretion characteristics in vivo, enabling lower dose rates.[3–5] Commonly available trifluoromethylated compounds are nonchiral aryl CF_3 and OCF_3 containing compounds, however, there has been recent interest in the application of products carrying the CF_3 group at a stereogenic center.[6–8] The number of available starting materials for such transformations is few hindering the development of methods for preparation of compounds with the CF_3 at a stereogenic center.[9–12] Trifluoroacetaldehyde (fluoral) is among the most useful CF_3 synthons that fueled the asymmetric synthetic developments,[13–15] including its chiral Friedel–Crafts reactions.[16,17] Enantiomerically pure trifluoro-1-(indol-3-yl)ethanols (TFIEs) are of particular interest as they are analogous to trifluoromethyl-indolyl-hydroxypropionic acid esters, which were found to be potent inhibitors of fibrillogenesis of Alzheimer's amyloid β (Aβ) peptide,[18–20] and fructose 1,6-biphosphatase enzyme, that is a frequent target of drug development for the type II diabetes.[21,22] The only method that describes preparation of enantiomerically enriched TFIEs applies an enzyme-catalyzed kinetic resolution.[23]

Enantioselective Friedel–Crafts reaction of indoles is a powerful tool to access a diverse pool of enantiopure indole derivatives. The most commonly applied catalysts for such transformations are metal-based chiral Lewis acids.[24] While these catalysts are usually effective and selective, metal-free catalytic systems appear preferable due to environmental concerns. In addition, the metal complex-based Lewis acid catalysts often include expensive synthetic ligands, are moisture and air sensitive and the reactions require inert atmosphere. Recent developments in enantioselective organocatalysis appear to provide solution for some of these problems.[25,26] Organocatalysts are usually based on natural products, that are commercially available and economic.[27,28] One particularly versatile group of compounds is the family of Cinchona alkaloids, which are known to be the catalyst of choice for many applications such as additions, substitutions, acylations, rearrangements, decarboxylations etc. providing excellent yields and stereoselectivity.[29,30]

Herein, extending our efforts in the development of sustainable synthetic methods we describe the first effective asymmetric organocatalytic synthesis of TFIEs via enantioselective Friedel–Crafts hydroxyalkylation of indoles with trifluoroacetaldehyde methyl hemiacetal.

EXPERIMENTAL

General Information

All reactions were carried out in closed vials without inert atmosphere. Solvents were purchased from Fisher and/or Aldrich and kept on MS 4 Å molecular sieves for at least 2 days before use. All reagents and catalysts were purchased from Aldrich except trifluoroacetaldehyde methyl hemiacetal, 7-ethylindole, 5-benzyloxyindole (Alfa Aesar) and two catalysts which were synthesized according to literature procedures: catalysts **5**[31] and **9**.[32] NMR spectra (^1H, ^{13}C, ^{19}F) were recorded on Varian-300 NMR spectrometer with tetramethylsilane, residual solvent signal and $CFCl_3$ as references. Reactions were monitored by gas chromatography/mass spectrometry with an Agilent 6850-5973N GC-MS system (30m DB-5 type column, 70 eV impact ionization). Chromatographic purifications were carried out using self-prepared preparative TLC plates (1.5 mm thickness, Aldrich silica gel with gypsum binder as stationary phase). The enantiomeric excess was determined using chiral high-performance liquid chromatography (HPLC) with Daicel Chiralcel OD-H, AS-H or OJ-H on columns a Jasco PU-2080/2070 HPLC system with UV detection at 260 nm.

Assignment of Absolute Configuration

The absolute configuration of the products was assigned on the basis of literature data.[23] The optical rotation of (*S*)-2,2,2-trifluoro-1-(indol-3-yl)ethanol in 97% enantiomeric excess is $[\alpha]^{20}_D = +14.5^\circ$ ($c = 0.5$,

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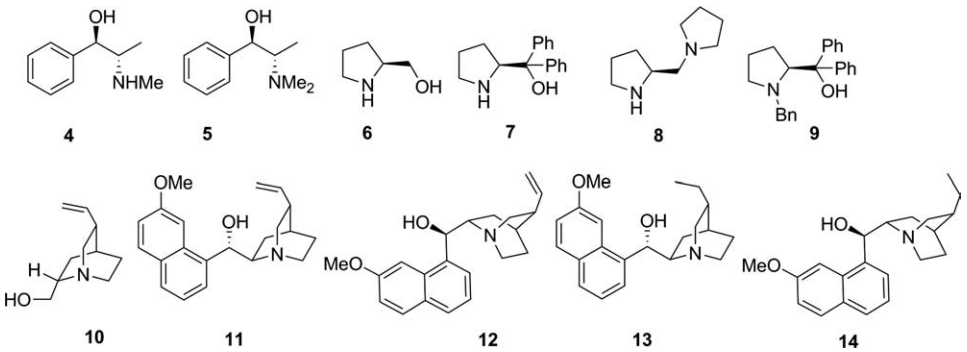


Fig. 1. Structures of chiral organocatalysts, used for asymmetric Friedel–Crafts hydroxyalkylation of indoles with trifluoroacetaldehyde methyl hemiacetal.

EtOH).[23] The measured optical rotation of **3a** in 58% enantiomeric excess is $[\alpha]^{20}_{D} = +8.2^{\circ}$ (c = 1.04, $CHCl_3$). Based on the data, the configuration was assigned to be (*S*) for all indole derivatives.

General Experimental Procedure for the Enantioselective Hydroxyalkylation of Indoles with Trifluoroacetaldehyde Methyl Hemiacetal

To solution of indole (58.5 mg, 0.5 mmol) and hydroquinine (48.9 mg, 0.15 mmol) in dry dichloromethane (0.5 ml), trifluoroacetaldehyde methyl hemiacetal (70 μl, 0.625 mmol) was added. The reaction mixture was kept in a tightly closed vial and stirred for the indicated period of time, and then analyzed by GC-MS to determine conversion. After completion, the product was purified using preparative TLC affording pure TFIE. Finally, all products were characterized by MS and NMR and the optical purity was determined by HPLC.

General Experimental Procedure for the Enantioselective Hydroxyalkylation of Indoles with Neat Fluoral

Fluoral was produced using a procedure described earlier.[33] The gas (approximately twofold excess) was condensed at −78°C in nitrogen atmosphere and solution of indole (58.5 mg, 0.5 mmol) and catalyst hydroquinine (32.6 mg, 0.1 mmol) in DCM (0.5 ml) was slowly added. After stirring for 5 minutes, the reaction mixture was allowed to warm to room temperature. The reaction mixture was kept in a tightly closed vial for the indicated period of time; the progress was determined by GC-MS. The crude product was purified by preparative TLC and the pure product was characterized by NMR. The optical purity was determined by HPLC.

(S)-2,2,2-trifluoro-1-(indol-3-yl)ethanol (3a). Colorless solid, mp.: 134–136°C. MS (EI, 70 eV); *m/z*: 197 (100%), 146 (86%), 215 (74%, M^+), 118 (71%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.25 (br s, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.16–7.41 (m, 4H), 5.31 (q, J = 6.9 Hz, 1H), 2.48 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 135.97, 126.67, 125.62, 123.81, 123.52, 122.89, 120.57, 119.24, 111.48, 67.47 (q, J = 33.5 Hz). ^{19}F NMR (300 MHz, $CDCl_3$): −77.82 (d, J = 6.9 Hz).

(S)-2,2,2-trifluoro-1-(5-fluoroindol-3-yl)ethanol (3b). Viscous oil. MS (EI, 70 eV); *m/z*: 164 (100%), 233 (71%, M^+), 136 (71%), 215 (45%), 109 (36%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.42 (br s, 1H), 7.32 (d, J = 9.9 Hz, 1H), 6.92–7.25 (m, 3H), 5.20 (q, J = 6.9 Hz, 1H), 3.26 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 159.64, 132.51, 125.62, 112.29, 112.16, 111.45, 111.10, 104.54, 104.22, 67.36 (q, J = 33.5 Hz). ^{19}F NMR (300 MHz, $CDCl_3$): −77.87 (d, J = 6.9 Hz).

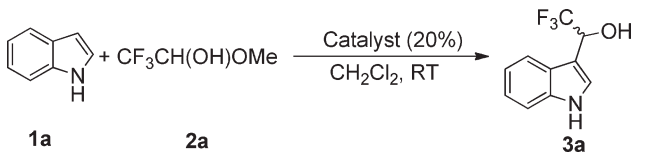
(S)-2,2,2-trifluoro-1-(5-chloroindol-3-yl)ethanol (3c). Colorless solid, mp.: 167–169°C. MS (EI, 70 eV); *m/z*: 180 (100%), 249 (70%, M^+), 117 (55%), 182 (35%), 231 (27%), 251 (23%, M^+). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.51 (br s, 1H), 7.63 (s, 1H), 7.12–7.25 (m, 3H), 5.19 (q, J = 6.9 Hz, 1H), 3.83 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 134.33, 125.30, 123.68, 123.08, 122.76, 119.42, 118.74, 112.55, 111.44, 67.18 (q, J = 33.5 Hz). ^{19}F NMR (300 MHz, $CDCl_3$): −77.84 (d, J = 6.9 Hz).

(S)-2,2,2-trifluoro-1-(5-bromoindol-3-yl)ethanol (3d). Colorless solid, mp.: 170–171°C. MS (EI, 70 eV); *m/z*: 225 (100%), 226 (92%), 117 (67%), 293 (64%, M^+), 295 (63%, M^+), 277 (51%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.41 (br s, 1H), 7.78 (s, 1H), 7.11–7.27 (m, 3H), 5.16 (q, J = 6.6 Hz, 1H), 3.35 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 134.57, 127.19, 126.47, 125.60, 125.14, 121.79, 113.63, 112.96, 108.72, 66.19 (q, J = 33.3 Hz). ^{19}F NMR (300 MHz, $CDCl_3$): −77.80 (d, J = 6.6 Hz).

(S)-2,2,2-trifluoro-1-(5-iodoindol-3-yl)ethanol (3e). Colorless solid, mp.: 143–144°C. MS (EI, 70 eV); *m/z*: 341 (100%, M^+), 272 (58%), 145 (55%), 144 (52%), 323 (28%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.34 (br s, 1H), 8.08 (s, 1H), 7.15-7.51 (m, 3H), 5.28 (q, J = 6.9 Hz, 1H), 2.59 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 135.08, 131.30, 128.31, 128.14, 126.47, 124.50, 122.74, 113.35, 84.19, 67.83 (q, J = 33.6 Hz). ^{19}F NMR (300 MHz, $CDCl_3$): −77.97 (d, J = 6.9 Hz).

(S)-2,2,2-trifluoro-1-(5-methoxyindol-3-yl)ethanol (3f). Viscous oil. MS (EI, 70 eV); *m/z*: 245 (100%, M^+), 176 (82%), 227 (43%), 148 (37%), 133 (33%). ^{1}H NMR (300 MHz, $(CD_3)_2CO$): δ (ppm) 10.36 (br s,

TABLE 1. Effect of catalysts on the enantioselective Friedel-Crafts hydroxyalkylation of indole with trifluoroacetaldehyde methyl hemiacetal



1a 2a 3a

Entry	Catalyst	C_{Indole} (M)	Time (h)	Yield (%)[a]	*ee* (%)[b]
1	No catalyst	1	96	45	0
2	**4**	0.5	48	95	0
3	**5**	1	48	98	0
4	**6**	0.5	48	20	0
5	**7**	0.5	48	97	0
6	**8**	0.5	96	80	9
7	**9**	0.5	48	95	0
8	**10**	1	48	97	0
9	**11**	0.5	96	80	19(*R*)
10	**12**	0.5	96	96	37(*S*)
11	**13**	1	96	97	39(*R*)
12	**14**	1	96	98	46(*S*)
13	**14**	2	96	>99	52(*S*)

[a]GC yield.
[b]Determined by HPLC.

TABLE 2. Effect of hydroquinine loading on the enantioselective Friedel-Crafts hydroxyalkylation of indole with trifluoroacetaldehyde methyl hemiacetal[a]

Entry	$C_{catalyst}$ (mol%)	Time (h)	Yield (%)[b]	*ee* (%)[c,d]
1	10	96	87	46
2	20	96	>99	52
3	30	72	>99	58
4	40	96	88	55
5	50	96	81	53

[a]2M of Indole in DCM, RT.
[b]GC yield.
[c]Determined by HPLC.
[d]In all products (*S*) enantiomer were formed in excess.

1H), 7.44 (s, 1H), 7.32 (d, J = 8.7 Hz , 1H), 7.25 (s, 1H), 6.80 (dd, ^1J = 8.7 Hz, ^2J = 2.4 Hz, 1H) 5.44 (q, J = 6.9 Hz, 1H), 3.80 (s, 3H), 3.25 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 154.30, 127.91, 125.23, 125.06, 124.18, 112.34, 112.28, 112.25, 101.29, 55.14, 66.89 (q, J = 25.1 Hz). ^{19}F NMR (300 MHz, $CDCl_3$): −77.19 (d, J = 6.9 Hz).

(S)-2,2,2-trifluoro-1-(7-ethylindol-3-yl)ethanol (3i). Colorless solid, mp.: 137–139°C. MS (EI, 70 eV); *m/z*: 174 (100%), 243 (84%, M^+), 118 (42%), 225 (34%), 224 (31%), 146 (29%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.23 (br s, 1H), 7.52 (d, J = 8.2 Hz, 1H), 7.05–7.20 (m, 3H), 5.24 (q, J = 6.9 Hz, 1H), 2.98 (br, 1H), 2.78 (q, J = 7.8 Hz, 2H), 1.30 (t, J = 7.8 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 134.84, 126.96, 126.71, 125.41, 123.48, 121.22, 120.77, 116.81, 109.87, 67.37 (q, J = 25.1 Hz), 23.75, 13.64. ^{19}F NMR (300 MHz, $CDCl_3$): −77.78 (d, J = 6.9 Hz).

(S)-2,2,2-trifluoro-1-(5-benziloxyindol-3-yl)ethanol (3k). Viscous oil. MS (EI, 70 eV); *m/z*: 91 (100%), 321 (20%, M^+), 230 (18%), 305 (17%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.20 (br s, 1H), 6.87–7.43 (m, 9H), 5.16 (q, J = 6.9 Hz, 1H), 5.02 (s, 2H), 3.00 (br, 1H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 153.47, 137.08, 131.30, 128.58, 128.53, 128.08, 127.96, 127.75, 124.61, 113.75, 112.26. 103.52, 102.71, 71.01, 67.10 (q, J = 24.4 Hz). ^{19}F NMR (300 MHz, $CDCl_3$): −77.67 (d, J = 6.9 Hz).

(S)-2,2,2-trifluoro-1-(5-methylindol-3-yl)ethanol (3l). Viscous oil. MS (EI, 70 eV); *m/z*: 211 (100%), 160 (65%), 229 (52%, M^+), 132 (47%), 210 (37%). ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 8.11 (br s, 1H), 7.45 (s, 1H), 7.04–7.22 (m, 3H), 5.19 (q, J = 6.9 Hz, 1H), 2.93 (br, 1H), 2.43 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 134.23, 129.96, 125.80, 124.98, 124.47, 123.97, 122.94, 118.65, 111.16, 67.34 (q, J = 33.3 Hz), 21.40. ^{19}F NMR (300 MHz, $CDCl_3$): −77.73 (d, J = 6.9 Hz).

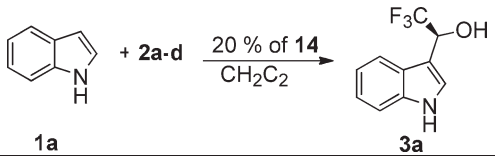
RESULTS AND DISCUSSION

Recently, it was observed in our laboratory that indole readily reacted with trifluoroacetaldehyde methyl hemiacetal under microwave conditions producing TFIE in good yield. Due to our interest in enantioselective organocatalytic Friedel–Crafts reactions with organofluorine electrophiles, the above observation initiated further exploration of this reaction, to develop an asymmetric catalytic reaction to synthesize enantiomerically pure products. To the best of our knowledge, the chiral target compounds have never been directly synthesized. In the only report describing these chiral compounds, enzymatic kinetic resolution was used to obtain the products.[18] First, the performance of several organocatalysts in the reaction was investigated. The group of catalysts studied included a chiral benzyl alcohol, several proline and Cinchona derivatives (Fig. 1). Such compounds are well-known organocatalysts.[29,34] The screening of different organocatalysts (Table 1) showed promising results in the reaction at room temperature. A comparative reaction without a catalyst resulted in 45% conversion after 96 h (entry 1). While the racemic reaction occurs without catalysis, all organocatalysts bearing the 1,2-aminoalcohol moiety increased the reaction rate. The inactivity in the only exception, prolinol (entry 4), can be explained by formation of a stable adduct with trifluoroacetaldehyde.[35] Catalysts **4**, **5**, **7**, and **9** showed the highest activity and short reaction times, however, produced racemic product. Overall, hydroquinine was found to be the best catalyst, providing the product with almost quantitative yield and *ee* of 52 % (entry 13).

Based on the data in Table 1, hydroquinine was selected as a catalyst for further studies, investigating the effect of hydroquinine concentration (Table 2). A decrease in concentration of the catalyst to 10 mol% led to lower yield and *ee* of product as compared to Table 1 entry 13. The increase in catalyst amount to 30 mol%, however, resulted in the products in quantitative yield and 58% *ee* (entry 3), after 72 h. Further increase in catalyst loading up to 50 mol% slowed down the reaction with no further increase in enantiomeric excess.

To further optimize reaction conditions, the different sources of fluoral as electrophile were evaluated. In addition to neat fluoral, different hemiacetals of trifluoroacetaldehyde can be used in this reaction (Table 3). Methyl, ethyl and

TABLE 3. Effect of different sources of trifluoroacetaldehyde on the enantioselective Friedel-Crafts hydroxyalkylation of indole[a]

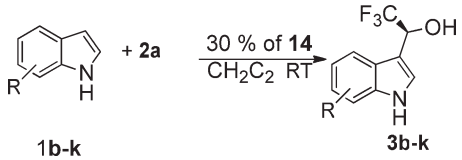


1a 3a

Entry	Trifluoroacetaldehyde source	Time (h)	Temp.	Yield (%)[b]	*ee* (%)[c]
1	$CF_3CH(OH)OMe$, **2a**	96	RT	97	46
2	CF_3CHO[d], **2b**	96	−78°C-RT	67	45
3	$CF_3CH(OH)OEt$ (90% water solution), **2c**	96	RT	96	43
4	$CF_3CH(OH)OEt$ (90% ethanol solution), **2c**	96	RT	97	45
5	$CF_3CH(OH)OBn$, **2d**	96	RT	96	45

[a]1M of indole in DCM.
[b]Isolated yield.
[c]Determined by HPLC.
[d]See text for details.

TABLE 4. Enantioselective hydroquinine-catalyzed Friedel-Crafts hydroxyalkylation of indoles with trifluoroacetaldehyde methyl hemiacetal[a]



Entry	*R*	Product	Yield (%)[b]	*ee* (%)[c]
1	5-H (**1a**)	**3a**	98	58
2	5-F (**1b**)	**3b**	96	68
3	5-Cl (**1c**)	**3c**	96	75
4	5-Br (**1d**)	**3d**	95	59
5	5-I (**1e**)	**3e**	95	47
6	5-MeO (**1f**)	**3f**	94	65
7	1-Me (**1g**)	**3g**	67	0
8	5-NO_2 (**1h**)	**3h**	No reaction	
9	7-Et (**1i**)	**3i**	92	46
10	5-BnO (**1k**)	**3k**	96	48
11	5-Me (**1l**)	**3l**	95	30

[a]Reaction time for all runs 72 h.
[b]Isolated yield.
[c]Determined by HPLC.

benzyl hemiacetals were applied to observe the steric effect of alkyl groups on the reaction. The reaction, including both yield and optical purity appeared to be nonsensitive to the steric demand of the alkyl group of acetal part of the reagents. Water and ethanol solution of trifluoroacetaldehyde ethyl hemiacetal gave the identical results as well. This indicates that the *O*-alkyl part does not participate in enantiodifferentiation step. This hypothesis was supported by data obtained by using neat fluoral **2b**, that was produced via a literature procedure.[33] The product was obtained with the same enantioselectivity, but in a lower yield (entry 1) possibly due to low yield of recovered fluoral.

The reaction, however, is very sensitive to different solvents. Nonpolar solvents such as hexane and toluene resulted in significantly lower enantioselectivity in the reaction, while ethanol, diethyl ether and other polar solvents inhibited the reaction completely. Only chlorinated solvents (dichloromethane and dichloroethane) provided good enantioselectivity and high product yield.

Based on the above studies optimized conditions for the reaction were determined and further studies were conducted using hydroquinine as a catalyst, trifluoroacetaldehyde methyl hemiacetal as a source of CF_3CHO and dichloromethane as a solvent, at room temperature.

The above mentioned optimum conditions were used in a reaction of substituted indoles to determine the scope of the reaction (Table 4). In most cases, the presence of moderate electron-withdrawing or electron-donating groups in the 5-position of indole resulted in higher enantioselectivity with *ee* up to 75% for 5-chloroindole (entries 2-4, 6). The enantioselectivity strongly depends on the size of the substituent and in the presence of large iodo- and benzyloxy-groups (entries 5, 10), the *ee* decreases compared to that of a nonsubstituted indole. *N*-methyl indole produced a racemic product, illustrating the crucial importance of the hydrogen connected to nitrogen in substrate-catalyst interactions (entry 7). Position 7, which is sterically close to the nitrogen as well, also negatively affects the enantioselectivity providing further support to the importance of hydrogen at position 1 (entry 9). The strong electron-withdrawing nitro group completely deactivates the indole resulting in no product formation (entry 8).

The absolute configuration of **3a**, which was prepared by hydroquinine catalysis, was determined by comparison of its optical rotation to literature data[23] and was assigned to be (*S*) for all indole derivatives. The catalyst can be recovered from the reaction mixture by acid-base extraction and used again without significant loss of activity.[36]

Some characteristic limitations of the procedure provide an idea of a possible mechanism of the reaction. These limitations are: (i) The *N*-position of the indole should be underivatized, having a hydrogen to observe enantioselectivity after the reaction; (ii) Cinchona alkaloids with substituents on their free OH or quinuclidine N, produce racemic products; (iii) 2-substituted indoles do not react with fluoral. Interestingly, the reaction of indole with trifluoroacetaldehyde methyl hemiacetal described here has the same limitations and features as the asymmetric organocatalytic reaction of indole and trifluoropyruvate published earlier.[37] Based on the similar experimental facts, it is suggested that both reactions have similar mechanisms. It is proposed that the weakly acidic indole N-H forms a complex with hydroquinine through a hydrogen bond. Then, the OH of hydroquinine activates the carbonyl of fluoral. During this step, the hydroquinine provides a chiral environment for enantiodifferentiation of prochiral sites of fluoral making the formation of (*S*)-isomer favored. The suggested intermediate (Fig. 2) involves a cyclic arrangement to form the product. The presence of substituents in the C-2 position of indole would disrupt this cycle and thus result in racemic or no product.

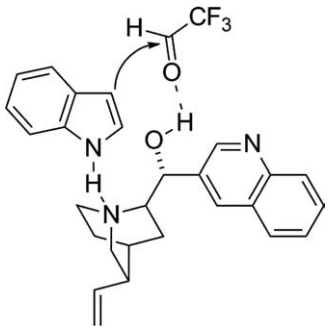


Fig. 2. Proposed enantioselection model for the enantioselective hydroxyalkylation of indoles with $CF_3-(R)C=O$ electrophiles.

CONCLUSION

The first direct asymmetric synthetic preparation of TFIEs from indoles and inexpensive trifluoroacetaldehyde methyl hemiacetal is described. The reaction was catalyzed by a well-known organocatalyst, hydroquinine and produced TFIEs in almost quantitative yield and *ee* up to 75% at room temperature. Based on the experimental data a mechanistic explanation is also provided.

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