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Organocatalytic Enantioselective Friedel–Crafts Alkylation of 1-Naphthol Derivatives and Activated Phenols with Ethyl Trifluoropyruvate

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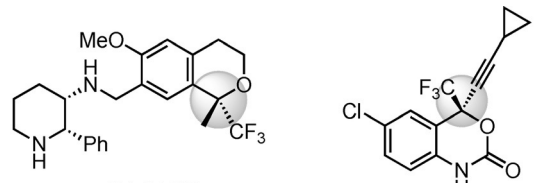
Abstract: An organocatalytic enantioselective Friedel–Crafts alkylation of a series of substituted 1-naphthol derivatives and activated phenols with ethyl trifluoropyruvate, catalyzed by a quinine-derived squaramide, is presented. Good yields and high to excellent enantioselectivities of the Friedel–Crafts alkylation products were obtained.

Keywords: asymmetric catalysis; Friedel–Crafts reaction; naphthols; organocatalysis; trifluoropyruvates

The Friedel–Crafts (F-C) reaction is one of the most fundamental, important and powerful C–C bond forming reactions in organic chemistry.[1] This reaction provides an efficient synthetic pathway to prepare functionalized aromatic compounds of great importance and widely used in academia and industry. Moreover, the catalytic enantioselective version of the F-C reaction leads to the formation of highly valuable chiral aromatic compounds.[2]

However, most of the examples reported in the literature with regard to this version are concerned with the use of heteroarenes such indoles and pyrroles as nucleophilic partners,[3] whilst other nucleophiles such as naphthols have been less studied, probably due to their reduced reactivity towards electrophiles.[4] Consequently, the extension of the asymmetric F-C alkylations to include naphthols is of great interest for organic synthesis. Since the first example of Erker in 1990[5] where the enantioselective alkylation of naphthol was described using an activated ketone such methyl pyruvate, only two asymmetric examples of the reaction between naphthols and ketones have been recently reported, using isatins as substrates.[6] Nevertheless, the enantioselective alkylation of 1-naphthol with alkyl trifluoropyruvates is not described, to the best of our knowledge. This reaction would provide access to chiral tertiary benzylic alcohols bearing a trifluoromethyl group as a substituent.[7,8] This particular motif has become an important structural characteristic in several drugs such as CJ-17493 or Efavirenz (Figure 1).[9]

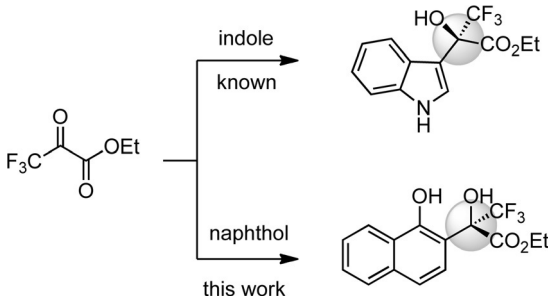


CJ-17493 (neurokinin 1 receptor antagonist) **Efavirenz** (anti-HIV)

Figure 1. Structures of drugs containing a chiral tetrasubstituted carbon bearing a trifluoromethyl group.

Since the pioneering work by Jørgensen and coworkers,[10] who described the alkylation of different aromatic and heteroaromatic compounds with alkyl trifluoropyruvate, several methodologies have been reported.[11] However, the enantioselective alkylation of naphthols with ethyl trifluoropyruvate remains elusive (Scheme 1).[12] As a part of our continuous interest in the enantioselective synthesis of CF_3-cointaining compounds,[13] herein we report an organocatalytic enantioselective F-C alkylation of 1-naphthol derivatives with ethyl trifluoropyruvate under mild conditions using a squaramide organocatalyst[14] derived from quinine.

The reaction of 1-naphthol (**1a**) with ethyl trifluoropyruvate (**2**) was studied with different bifunctional

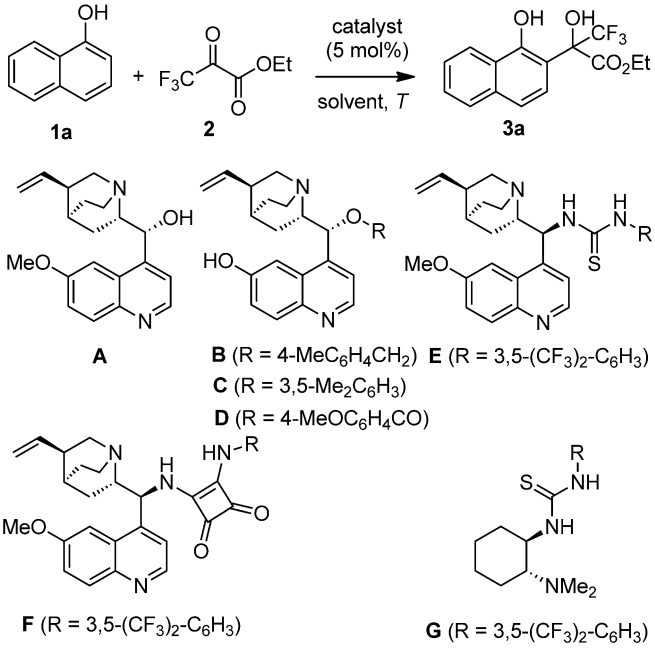


Scheme 1. Enantioselective Friedel–Crafts alkylation with ethyl trifluoropyruvate.

organocatalysts under various reaction conditions (Table 1). We initially examined quinine (**A**) in toluene at room temperature (entry 1, Table 1). To our delight, the corresponding tertiary alcohol **3a** was obtained smoothly in 70% yield and 43% *ee*. 9-*O*-(*p*-$MeC_6H_4CH_2$)-cupreine **B**, where the 9-OH group was protected and the 6′-OH was free, showed an inversion of the enantioselectivity (48% *ee*), with a moderate yield (Table 1, entry 2). Although cupreine catalysts **C** and **D**, with different groups such as aryl ether or benzoyl group at the 9-OH position, afforded the product **3a** with higher enantioselectivity, (78% *ee*, entries 3 and 4) the reactions were slower. When quinine-derived thiourea **E** was used (Table 1, entry 5), the reaction proceed faster, furnishing the product in 86% yield, although with a decrease in the enantiomeric excess (46%). Quinine-derived squaramide **F** proved to be the most efficient catalyst (entry 6, Table 1) in terms of yield (89%) and enantioselectivity (78% *ee*). Other thiourea organocatalysts bearing a tertiary amine moiety, such as Takemoto's catalyst **G** (entry 7, Table 1), showed good yield (86% yield), although with decreased selectivity (46% *ee*). We decided to study the effect of different solvents (entries 8–12) with catalyst **F** in the Friedel–Crafts alkylation. To our delight, when ether was used as a solvent, excellent results were obtained (92% yield, 91% *ee*, entry 9). The enantiomeric excess of tertiary alcohol **3a** could reach 97% (entry 13) when the reaction was carried out at 0 °C. Finally, the catalyst loading was decreased to 2 and then 1 mol% (entries 14 and 15, respectively), with similar results in terms of enantioselectivity, although the reactivity was much lower.

Under the optimized conditions shown in entry 13, the substrate scope was investigated (Scheme 2). Different 1-naphthols[15] substituted with electron-withdrawing and electron-donating groups were reacted with ethyl trifluoropyruvate[16] (**2**). The presence of an electron-donating group such MeO at the position 4 decreased the yield, without compromising the enantiomeric excess (96%), however, groups such as Cl, Br and OAc at this position gave good yields and excellent enantioselelectivities. Moreover, the reaction

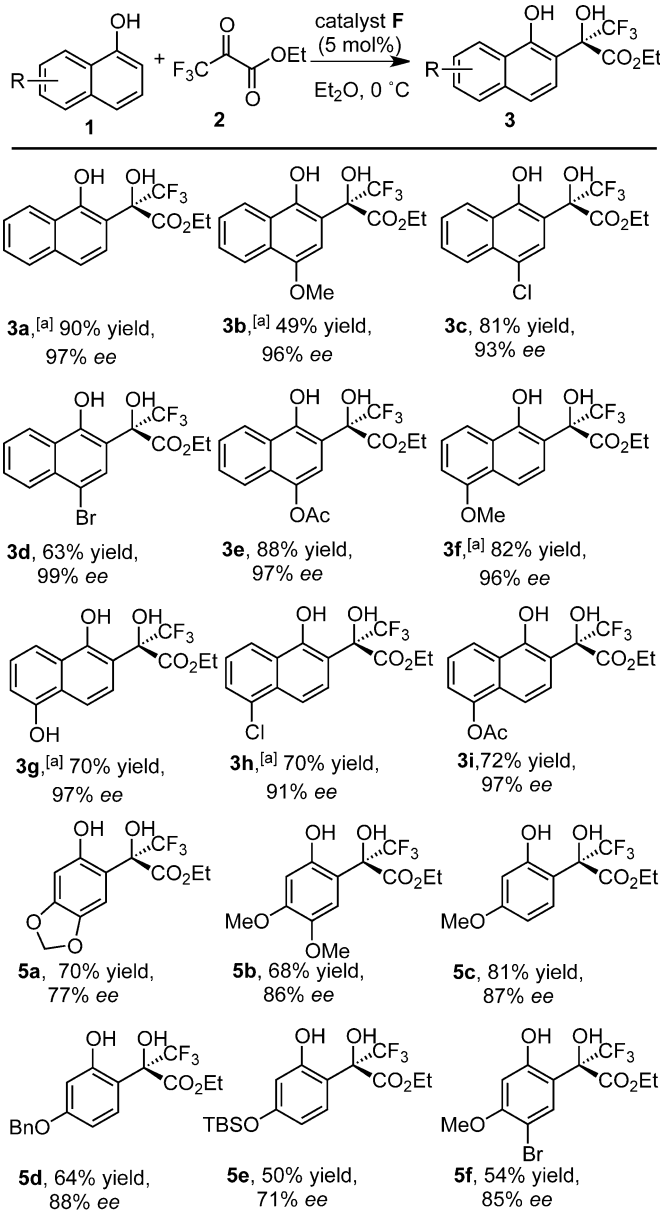
Table 1. Optimization of the reaction conditions.[a]



Entry	Catalyst (mol%)	Solvent	*t* [h]	*T* [°C]	Yield [%][b]	*ee* [%][c]
1	**A** (5%)	toluene	2	r.t.	70	43[d]
2	**B** (5%)	toluene	3	r.t.	54	48
3	**C** (5%)	toluene	7	r.t.	64	78
4	**D** (5%)	toluene	6	r.t.	66	78
5	**E** (5%)	toluene	1.5	r.t.	86	46
6	**F** (5%)	toluene	1.5	r.t.	89	78
7	**G** (5%)	toluene	2	r.t.	86	46[d]
8	**F** (5%)	CH_2Cl_2	1	r.t.	91	80
9	**F** (5%)	Et_2O	2	r.t.	92	91
10	**F** (5%)	EtOAc	2	r.t.	88	87
11	**F** (5%)	(*i*-Pr)$_2$O	2	r.t.	94	87
12	**F** (5%)	MTBE	24	r.t.	30	91
13	**F** (5%)	Et_2O	2	0	90	97
14	**F** (2%)	Et_2O	24	0	80	98
15	**F** (1%)	Et_2O	24	0	35	96

[a] *Reaction conditions:* 0.100 mmol **1a**, 0.125 mmol **2**, and catalyst in solvent (1.0 mL).
[b] Isolated yield after column chromatography.
[c] Enantiomeric excess determined by chiral HPLC.
[d] The major product is the (*S*)-enantiomer.

was studied with 1-naphthol substituted at the 5-position, with good yields and excellent enantiomeric excesses. Remarkably, 1,5-dihydroxynaphthalene reacted smoothly affording the corresponding chiral tertiary alcohol **3g** with 70% yield and 97% *ee*.[17] Finally, our reaction protocol also allowed us to use electron-rich phenols as nucleophiles.[18] Sesamol[19] (**4a**), 3,4-dimethoxyphenol (**4b**) and even phenols with only one electron-donating group (**4c–4f**) gave the corresponding chiral tertiary alcohols (**5a–5f**), although a decrease in the enantioselectivity was observed. Un-



[a] Compounds **3a**, **3b**, **3f**, **3g** and **3h**, were isolated with a minor impurity that corresponds to the lactone.

Scheme 2. Substrate scope for the enantioselective Friedel–Crafts alkylation. *Reaction conditions:* 0.100 mmol **1**, 0.125 mmol **2**, and **F** (5 mol%) in Et_2O (1.0 mL) at 0 °C. Isolated yield after column chromatography. Enantiomeric excess determined by chiral HPLC.

fortunately, simple phenol is unreactive in our reaction conditions.

The absolute configuration of product **3c** was assigned as (*R*) on the basis of an X-ray crystal structure analysis (Figure 2).[20] The configurations of the rest of products were assigned on the assumption of a uniform mechanistic pathway.

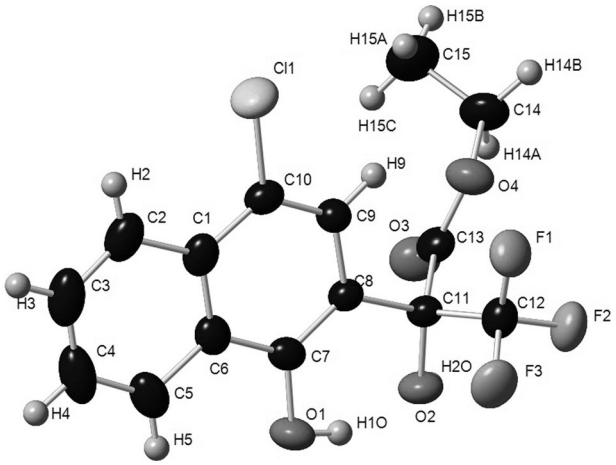
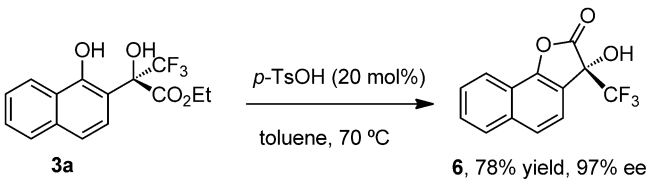


Figure 2. X-ray crystal structure of **3c**.[20]

Treatment of product **3a** with *p*-TsOH in toluene at 70 °C afforded chiral lactone[21] **6** in 80% yield and preserving the enantiomeric purity of the compound (Scheme 3).



Scheme 3. Lactonization of **3a**.

In summary, we have developed a highly enantioselective addition of 1-naphthol derivatives to ethyl trifluoropyruvate employing a squaramide organocatalyst derived from quinine. The corresponding chiral tertiary alcohols bearing a trifluoromethyl group were obtained with good yields and excellent enantioselectivities. Furthermore, the methodology was extended to the use of activated phenols, with good yields and enantiomeric excesses.

Experimental Section

General Friedel–Crafts Procedure

Naphthol **1** (0.100 mmol), ethyl trifluoropyruvate **2** (0.125 mmol) and squaramide **F** (2.4 mg, 0.050 mmol) were dissolved in 1.0 mL of ether and the mixture stirred at 0 °C until the reaction was complete (TLC). Finally, the reaction mixture was directly applied to column chromatograpy, using hexane:Et_2O (95:5) as eluent to afford product **3**.

Synthesis of (*R*)-3-Hydroxy-3-(trifluoromethyl)-naphtho[1,2-*b*]furan-2(3*H*)-one (6)

A solution of **3a** (30 mg, 0.095 mmol) and *p*-TsOH (4 mg, 0.019 mmol) in toluene (0.4 mL) was stirred for 6 h at 70 °C.

The corresponding reaction mixture was purified directly by flash chromatography on silica gel affording compound **6**; yield: 19.8 mg (78%).

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[15] 2-Naphthol was unreactive under the reaction conditions, probably due to steric hindrance.

[16] Methyl trifluoropyruvate was tested under the reaction conditions, but a mixture of α-hydroxy-α-CF_3-ester and lactone (1:1.2 by ^{19}F NMR) was observed, see the Supporting Information for further details.

[17] Compounds **3a**, **3b**, **3f**, **3g** and **3h** were isolated with a minor impurity that has been identified as the corresponding lactone. This lactone is formed during the course of the reaction, but we also observed the formation of the lactone during the isolation and purification processes of the product. This lactone has been fully characterized for the cyclization product of compound **3a**, see Scheme 3.

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