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Organocatalytic Enantioselective Functionalization of Hydroxyquinolines through an aza-Friedel-Crafts Alkylation with Isatin-derived Ketimines

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Abstract. A highly enantioselective addition of hydroxyquinolines to isatin-derived ketimines has been realized using a quinine-derived thiourea organocatalyst. The reaction affords chiral 3-amino-2-oxindoles bearing a quinoline moiety with a quaternary stereocenter in high yields (up to 98%) and excellent enantioselectivities (up to 99%). Moreover, we can extend this methodology for the enantioselective functionalization of 5-hydroxyisoquinoline. This methodology represents, to the best of our knowledge, the first enantioselective addition of hydroxyquinolines to imines.

Keywords: asymmetric organocatalysis ; Friedel-Crafts reaction; isatin-derived ketimines ; quinoline; thiourea

Nitrogen-containing aromatic heterocycles are ubiquitous in agrochemicals, pharmaceuticals and natural products.[1] Therefore, the synthesis of chiral nitrogen heterocycles represents a hot topic in organic chemistry due to the great synthetic and industrial interest of such compounds. In this context, quinoline[2] or 1-aza-naphthalene is one of the most important aza-aromatic compounds because of the wide range of biological activities of their derivatives. The quinoline scaffold is present in numerous natural products,[3] such as the alkaloid quinine used to treat malaria and babesiosis, or its diastereoisomer quinidine with antiarrhythmic activity; quinoline is also present in synthetic drugs such as primaquine, an alternative medication to treat and prevent malaria. Quinoline-pyridone hybrids, both natural (camptothecin) as synthetic derivatives (topotecan) present cytotoxic activity and are used as a chemotherapeutic agents (Figure 1A).
The ubiquity of the quinoline scaffold has prompted the development of several efficient methodologies for the functionalization of quinolines.[4] In this context, the electrophilic enantioselective functionalization of the quinoline ring has been scarcely studied, in contrast to the nucleophilic functionalization of quinoline ring broadly investigated in the literature.[5] In order to accomplish the electrophilic functionalization of the quinoline carbocyclic ring, we planned to use the activating/directing effects of a hydroxyl group in the carbocyclic ring.[6] This strategy was used by the group of Jørgensen in 2006,[7] for the diastereoselective atropoisomeric functionalization at 5' position of the quinoline core of cupreine derivatives by an amination reaction.

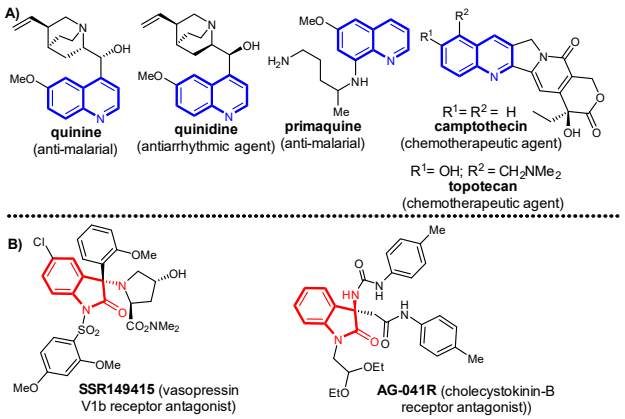


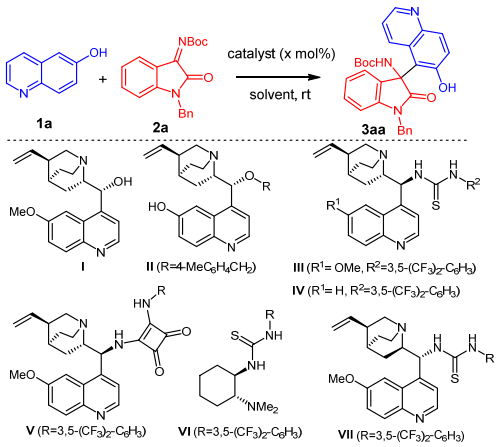
Figure 1. Examples of biologically active quinoline compounds and 3-substituted 3-amino-2-oxindoles.

However, this strategy has not been used for the enantioselective functionalization of hydroxyquinolines, to the best of our knowledge. In view of this, we decided to study the enantioselective aza-Friedel-Crafts reaction with imines, given the importance of the development of the asymmetric synthesis of chiral amines.[8] Recently, an aza-Friedel-Crafts reaction with 8-hydroxyquinoline has been described. However, this approach was reported for the synthesis of racemic Betti bases.[9] In this

communication, we have chosen Boc-protected isatin-derived ketimines as electrophiles,[10] which provided enantioenriched tetrasubstituted 3-aminooxindoles.[11] Remarkably, this motif is present in several biologically active compounds such as those shown in Figure 1B.[12,13] As a part of our ongoing interest in the asymmetric synthesis of chiral tetrasubstituted 3-aminooxindoles,[14] herein we present the first enantioselective addition of hydroxyquinolines to isatin-derived ketimines catalyzed by a thiourea bifunctional organocatalyst.

We chose the reaction of 6-hydroxyquinoline **1a** with isatin-derived *N*-Boc ketimine **2a** as a model reaction to screen various bifunctional organocatalysts. Bifunctional organocatalyst have been choosen considering the significant advantages of this kind of catalyst in asymmetric catalysis,[15] and we assume that the double-activation mode of hydrogen bonding and a Brønsted base could be essential to promote the aza-Friedel-Crafts aminoalkylation of hydroxyquinolines.

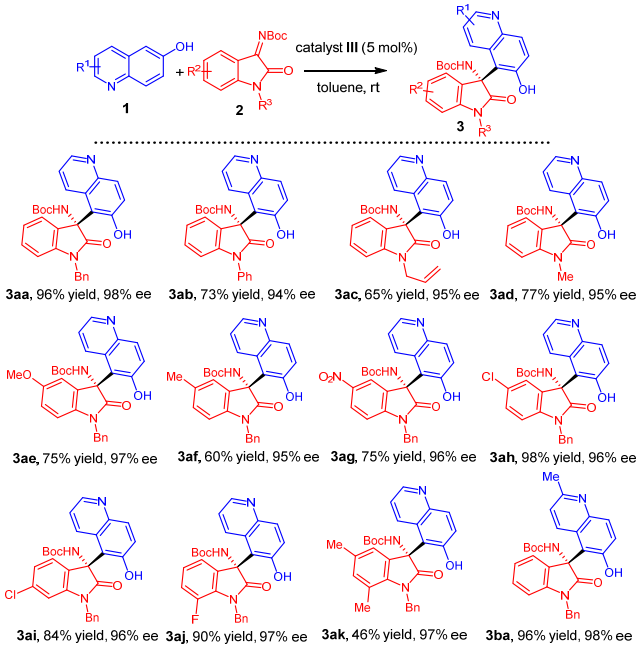
Table 1. Optimization of the reaction conditions.[a]



Entry	Cat. (x %)	t(h)	Solv.	Y. (%)[b]	ee (%)[c]
1	**I** (10 %)	95	Tol.	66	15
2	**II** (5 %)	30	Tol.	15	89
3	**III** (5 %)	45	Tol.	96	98
4	**IV** (5 %)	29	Tol.	74	98
5	**V** (5 %)	22	Tol.	55	99
6	**VI** (5 %)	24	Tol.	56	93[d]
7	**III** (5 %)	45	EtOAc	94	95
8	**III** (5 %)	45	THF	58	93
9	**III** (5 %)	45	CH_2Cl_2	90	92
10	**III** (2 %)	45	Tol.	57	98
11	**III** (1 %)	45	Tol.	25	96
12	**VII** (5 %)	45	Tol.	65	97[d]

[a] Reaction conditions: 0.1 mmol **1a**, 0.1 mmol **2a**, and catalyst in dry solvent (1.5 mL) at rt. [b] Isolated yield after column chromatography. [c] Enantiomeric excess determined by chiral HPLC. [d] Opposite enantiomer.

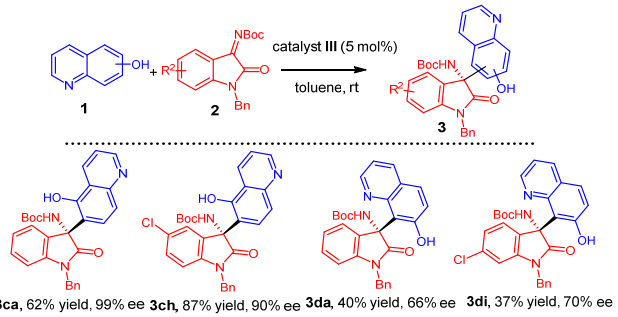
Quinine (**I**) could catalyze the reaction to obtain the product **3aa** with 66% yield after 6 days (Table 1, entry 1), however the product was obtained with low enantiomeric excess (15 % ee). Cupreine derivative **II** showed high enantioselectivity (89% *ee*), but the yield was very low[16] (15%, Table 1, entry 2). To our delight, when quinine-derived thiourea **III** was used (Table 1, entry 3), the reaction proceed smoothly with excellent results. The chiral quinoline **3aa** was obtained with 96% yield and 98% *ee*, after 2 days. When cinchonidine-derived thiourea **IV** was tested as catalyst, product **3aa** was afforded with the same enantiomeric excess but lower yield (74%). Quinine-derived squaramide **V**, showed excellent enantioselectivity (99% ee), although with moderate yield (56%).[16] Other thiourea organocatalyst bearing a tertiary amine moiety, such as Takemoto's catalyst **VI**, proved to be an efficient catalyst in terms of enantioselectivity (93% *ee*), though with a decreased yield (Table 1, entry 6). Therefore we chose catalyst **III** to continue further optimization. Other solvents such as EtOAc, THF or CH_2Cl_2, were also screened, but slightly lower enantioselectivities were observed (entries 7-9). The aza-Friedel-Crafts product **3aa** could be also achieved with good enantiomeric excess when only 2 or 1 mol% of catalyst was used (entry 10 and 11, respectively), although with lower yields. Furthermore, the opposite enantiomer of **3aa**, was achieved with excellent enantioselectivity (97% ee, entry 12), when quinidine-derived thiourea **VII** (5 mol%) was used as a catalyst.



Scheme 1. Scope of the aza-Friedel-Crafts reaction of 6-hydroxyquinolines with **2**. Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol), and catalyst **III** (5 mol%) in dry toluene (1 mL) at rt for 45 h.

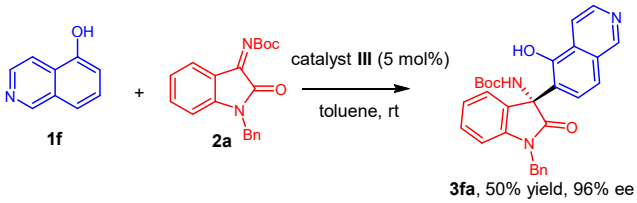
With the optimized reaction conditions in hand (entry 3, Table 1), we proceeded to study the scope of the aza-Friedel-Crafts reaction of 6-hydroxyquinolines with ketimines **2** (Scheme 1). Initially, substitution at the

N1 of the oxindole was evaluated (Scheme 1, **3 aa-3 ad**). Groups such as benzyl, phenyl, allyl or methyl were well tolerated, providing the corresponding products with high enantioselectivities (94-98 % *ee*). Next, we evaluated different *N*-Boc ketimines derived from various substituted *N*-benzylisatines. Electron-donating (MeO or Me) or electron-withdrawing (NO_2 or Cl) groups were tolerated at the 5-position of the isatin-derived ketimine, affording the corresponding products (**3ae-3ah**) with good yields and high enantioselectivities. Moreover, ketimines with substituents at 6- or 7-positions reacted smoothly, providing the aminoalkylated hydroxyquinolines **3ai** and **3aj** with good results. Moreover, the disubstituted ketimine **2k** could be used, obtaining the corresponding product **3ak** with excellent enantiomeric excess (97%), but moderate yield (46%). 6-hydroxyquinaldine **1b** could also be applied under the optimized reaction conditions giving **3ba** with excellents results (96% yield, 98% ee).



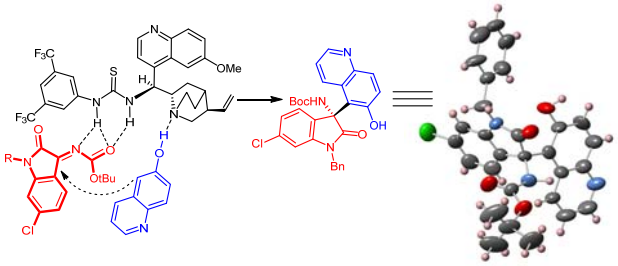
Scheme 2. Scope of the aza-Friedel-Crafts reaction of hydroxyquinolines with **2**. Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol), and catalyst **III** (5 mol%) in dry toluene (1.5 mL) at rt for 45 h.

After having proved the efficiency of our methodology for the enantioselective aza-Friedel-Crafts alkylation of 6-hydroxyquinoline at the C-5 position of the carbocyclic ring, we studied the scope of the reaction with other hydroxyquinolines bearing a hydroxy group in other positions of the carbocyclic ring (Scheme 2). Our goal was to achieve the enantioselective functionalization of every position in this ring by simply changing the position of the directing group. When 5-hydroxyquinoline (**1c**) was used as nucleophile under the optimized reaction conditions, with ketimine **2a** and **2h**, products **3ca** and **3ch**, substituted at C-6 were obtained with good yields and high enantiomeric excesses. 7-Hydroxyquinoline (**1d**) was also applied, although we observed a diminished reactivity and enantioselectivity. The 7-hydroxyquinoline was regioselectively alkylated at C-8, with ketimines **2a** and **2i**, with moderate yields and moderate enantiomeric excesses. Finally, when 8-hydroxyquinoline was used as nucleophile, we could not observed any reaction products. We attribute the lack of the reactivity of 8-hydroxyquinoline to an intramolecular hydrogen bonding between the hydroxyl group and the nitrogen atom from the quinoline.



Scheme 3. Aza-Friedel-Crafts reaction of 5-hydroxyisoquinolines with **2a**. Reaction conditions: **1f** (0.1 mmol), **2a** (0.1 mmol), and catalyst **III** (5 mol%) in dry toluene (1 mL) at rt for 45 h.

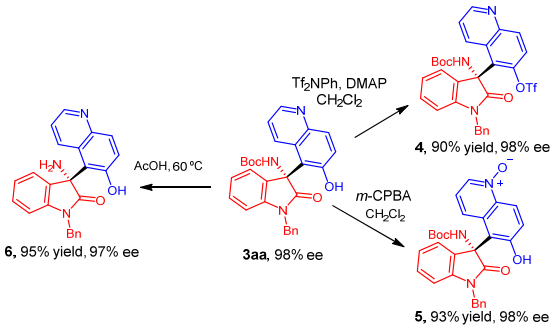
Isoquinoline scaffold is also an important nitrogen heterocycle that is present in a wide range of natural products and pharmaceuticals.[17] In view of the importance of isoquinoline structure, we decide to explore our methodology with the aza-Friedel-Crafts reaction of a hydroxyisoquinoline, in order to enantioselectively functionalize the carbocylic ring. Thus, 5-hydroxyisoquinoline **1f** was used as a nucleophile under the optimized reaction conditions (Scheme 3), and the corresponding product **3fa**, regioselectively alkylated at C-6, was obtained with an excellent 96% ee, but moderate yield (50%).



Scheme 4. Plausible transition-state model and X-ray crystal structure of **3ai**.

The absolute configuration of the stereogenic centre in compound **3ai** was determined to be (*R*) on the basis of X-ray crystallographic analysis (Scheme 4); the configuration of the rest of the products **3** were assigned on the assumption of a uniform mechanistic pathway.[18] A plausible transition-state model is depicted in Scheme 4. The thiourea catalyst is the responsible for the preorientation and the activation of the substrates acting as bifunctional organocatalyst. While the isatin-derived *N*-Boc-ketimine is activated upon formation of hydrogen bonds between the *N*-Boc group and the thiourea moiety of the catalyst, the hydroxyquinoline undergoes nucleophilic activation by hydrogen bonding with the quinuclidine moiety of the catalyst.[19,20] The quinoline will be directed to the *Re*-face of the ketimine, thus accounting for the observed enantioselectivity.

Additionally, different synthetic transformations were conducted with compound **3aa**, proving the utility of the developed methodology (Scheme 5). Compound **3aa** was transformed into triflate **4** with good yield preserving the enantiomeric purity. Hydroxyquinoline derivative **3aa** was also easily transformed into *N*-oxide **5** by oxidation with *m*-CPBA in CH_2Cl_2. Finally, removal of the Boc group in **3aa** was achieved by heating in acetic acid at 60 ºC affording the free amine **6** in 95% yield without loss of the stereochemical purity.



Scheme 5. Synthetic transformations.

In conclusion, we have developed an enantioselective aza-Friedel–Crafts reaction of hydroxyquinolines with isatin-derived ketimines, using a quinine-derived thiourea organocatalyst, obtaining the corresponding chiral 3-aminooxindoles with good yields and excellent enantioselectivities (up to 99% ee). This approach enables the introduction of substituents in positions C-5, C-6 or C-8 of the carbocyclic ring of quinoline in a regioselective manner, by just switching the position of the activating/directing hydroxy group. Furthermore, 5-hydroxyisoquinoline was enantioselectively alkylated with good results. Moreover, several transformations have been carried out with the products obtained. We envision that this procedure provides a successfully approach for the enantioselective functionalization of the carbocyclic ring of quinolines.

Experimental Section

General procedure for the enantioselective aza-Friedel-Crafts of hydroxyquinolines 1 and ketimines 2

In a 10 mL round bottom flask, hydroxyquinoline **1** (14.5 mg, 0.1 mmol), ketimine **2** (0.1 mmol), catalyst **VI** (3.0 mg, 0.005 mmol, 0.05 eq) and a stir bar were placed. The flask was purged with N_2 and toluene (1 mL) was added via syringe. The mixture was stirred at room temperature until completion (TLC). Finally, the reaction mixture was directly poured into a column for chromatography, using hexane:EtOAc or CH_2Cl_2: MeOH as eluents to afford product **3**.

Synthesis and characterization data for compound 4

Compound **3aa** (48.1 mg, 0.1 mmol) and 4-dimethylaminopyridine (36.8 mg, 0.3 mmol, 3 eq) were placed in a 10 mL round bottom flask. Then, the flask was purged with N_2 and CH_2Cl_2 (1 mL) was added. After 5 minutes, *N*-phenyl-bis(trifluoromethanesulfonimide (71.5 mg, 0.2 mmol, 2 eq) was added and the mixture was stirred at room temperature. The reaction was monitored by TLC. When the starting material was consumed, H_2O was added (5 mL) and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL) and dried under anhydrous Na_2SO_4. The organic solvents were removed under reduced pressure and the residue was purified by column chromatography being eluted with hexane: AcOEt (90:10 to 60:40).

Synthesis and characterization data for compound 5

Compound **3aa** (48.1 mg, 0.1 mmol) and *meta*-Chloroperoxybenzoic acid (17.3 mg, 0.2 mmol) were dissolved in 1 mL of CH_2Cl_2 and the mixture was stirred at room temperature. The reaction was monitored by thin layer chromatography being eluted with Hexane:AcOEt. When the starting material was consumed, the solvent was removed, and the crude mixture was dissolved in CH_2Cl_2 and poured directly to the column chromatograpy, using hexane:AcOEt (90:10 to 60:40)as eluent to afford product **5.**

Synthesis and characterization data for compound 6

Compound **3aa** (40 mg, 0.08 mmol) was dissolved in AcOH (2 mL). The solution was stirred at 60 ºC until completion. Then, the reaction was quenched with a saturated aquous $NaHCO_3$ solution and extracted with CH_2Cl_2 (3x30 mL). After drying the organic phase over $MgSO_4$ and evaporation of the solvent, the residue was purified by column chromatography being eluted with CH_2Cl_2: MeOH (100:0 to 95:5).

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