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Organocatalytic Enantioselective Functionalization of Indoles in the Carbocyclic Ring with Cyclic Imines.

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An organocatalytic enantioselective functionalization in the carbocyclic ring of indoles with benzoxathiazines 2,2-dioxides is described using a quinine-derived bifunctional organocatalyst. This aza-Friedel-Crafts reaction provides 4-indolyl, 5-indolyl and 7-indolyl sulfamidates derivatives in good yields (up to 99%) and with moderate to high enantioselectivities (up to 86% ee).

Introduction

The catalytic asymmetric Friedel-Crafts reaction[1] of aromatic compounds to imines is one of the most important methodologies for the synthesis of enantiopure chiral benzylic amines, which are present in a wide range of pharmaceuticals and natural products.[2] In this context, the enantioselective addition of indoles to imines is one of the most studied asymmetric Friedel-Crafts reactions,[3,4] due to the importance of indole scaffold in natural product synthesis, medicinal and agrochemical industry and material science.[5] However, the majority of methods on the enantioselective aza-Friedel-Crafts reaction of indoles involve the functionalization of C-3 position.[4] Additionally, different examples of the asymmetric functionalization at C-2 position of indoles with imines have been described.[6] In contrast, the enantioselective functionalization in the carbocyclic ring of indoles is hardly studied in the literature and represents a great challenge in asymmetric catalysis (Figure 1A).[7] We have recently presented a methodology for the organocatalytic enantioselective functionalization of the carbocyclic ring of indoles using as an activating/directing group a hydroxy group.[8-10] Hydroxyindoles, in the presence of bifunctional organocatalysts, react as phenols, even when the positions in the azole ring remained unsubstituted. Given the remarkable significance of chiral indoles bearing a nitrogen in α-position and hydroxyindoles (Figure 1B), the development of new methodologies for the synthesis of chiral indolyl amines is the great interest for organic synthesis.

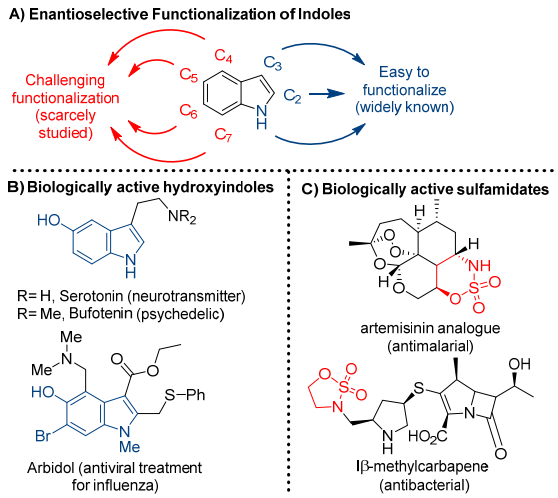

Figure 1 Enantioselective functionalization of indoles. Examples of biologically active hydroxyindoles and sulfamidates.

In this communication, to accomplish the enantioselective functionalization in the carbocyclic ring of indoles, we have chosen cyclic imines (benzoxathiazines 2,2-dioxides) as electrophiles. Very recently, the benzoxathiazines 2,2-dioxides have attracted the attention in asymmetric catalysis, because these compounds have been proved to be a powerful building blocks for the synthesis of chiral benzosulfamidate heterocycles. In this context, several sulfamidates have shown important biological activities[11] (Figure 1C) and several examples of enantioselective reactions have been described using these cyclic imines as electrophiles.[12] However, the number of enantioselective aza-Friedel-Crafts reactions using benzoxathiazines 2,2-dioxides is scarce.[13-14] In 2017, Kim have described the organocatalytic enantioselective alkylation of indoles at the C-3 position with cyclic imines catalyzed by chiral Brønsted phosphoric acid (Scheme 1A).[13a] The corresponding 3-indolyl sulfamidates derivatives were obtained with excellent yields and enantioselectivities. Herein, we described a complementary methodology to obtaining chiral indolyl

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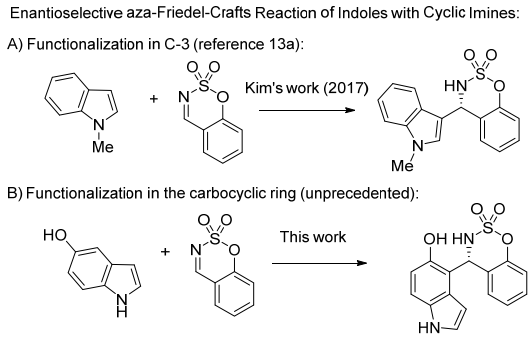
sulfamidates (Scheme 1B). By using a quinine-derived bifunctional organocatalyst, we achieve the functionalization of the carbocyclic ring of hydroxyindoles with cyclic imines, obtaining 4-indolyl, 5-indolyl and 7-indolyl sulfamidates derivatives (Scheme 1B).



Scheme 1. Enantioselective aza-Friedel-Crafts reaction of indoles with cyclic imines.

Results and discussion

We chose the aza-Friedel-Crafts reaction between benzoxathiazines 2,2-dioxides (**1a**) and 4-hydroxyindole (**2**) for the optimization studies. Different bifunctional organocatalysts derived from *Cinchona* alkaloids (Figure 2) in CH_2Cl_2 at room temperature were screened (Table 1). When quinine (**I**) was tried as catalyst, the regioselectivity was poor and we observed 3 compounds after 21 h of reaction (Table1, entry 1). The major product was the corresponding hydroxyindole alkylated at C-5 position (**3a**) in 48% yield but as a racemic mixture. Then, we isolated as an inseparable mixture after column chromatography, the product alkylated at C-7 position (**4a**) and the double alkylated product at C-5 and C-7 position (**5a**, a mixture of diasteroisomers in 1:1 ratio determined by ^{1}H NMR). Different bifunctional organocatalyst such cupreines, thioureas and squaramides were tested,[15] but we found that 9-O-benzylcupreine (**II**), derived from quinine, was the only one with a promising enantioselectivity (33% ee, entry 2). However, product **5a** was still obtained with high quantity (28%). We tried several cupreine derivatives with a variety of substituents on the secondary hydroxyl group. The best catalyst in terms of enantioselectivity was catalyst **XI**, giving compound **3a** in 48% yield, 43% ee in 6 h (entry 11).

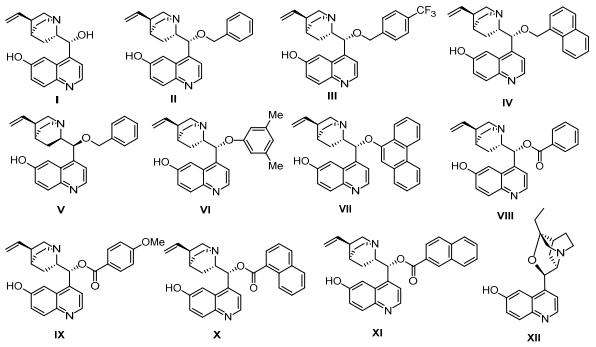
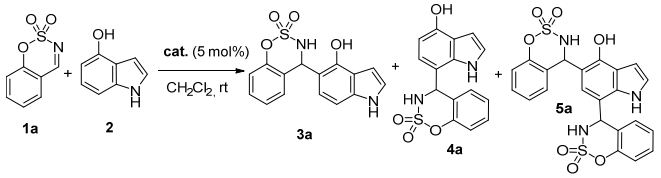


Figure 2 Bifunctional organocatalysts screened.

Table 1 Optimization of the reaction conditions.[a]

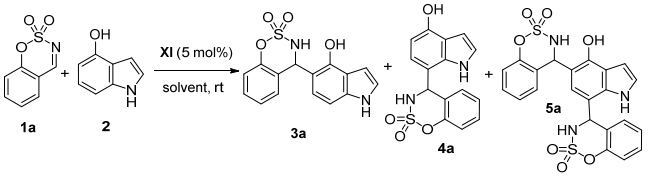


Entry	Catalyst (5 mol %)	t (h)	**3a** Yield (%)[b]	**3a** ee (%)[c]	**4a** Yield (%)[d]	**5a** Yield (%)[d,e]
1	**I**	21	48	0	6	34
2	**II**	24	57	33	9	28
3	**III**	5	56	31	8	23
4	**IV**	16	39	33	10	36
5	**V**	6	42	-8	8	30
6	**VI**	6	60	35	[11]	26
7	**VII**	6	58	42	10	21
8	**VIII**	24	39	33	10	36
9	**IX**	24	47	41	14	29
10	**X**	16	49	36	8	22
11	**XI**	6	48	43	15	24
12	**XII**	6	45	13	9	32

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol) and catalyst (5 mol%) in 1 mL of CH_2Cl_2 at room temperature. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] Determined by ^{1}H NMR. [e] The dr of compound **5a** was around 1:1 in all cases, determined by ^{1}H NMR.

Next, we examined different solvents (Table 2), obtaining the best enantioselectivities with chlorinated solvents. Specially, when the reaction was run in 1,2-dichloroethane compound **3a** was gained with 57% ee (entry 3, Table 2). Then, the effect of the reaction temperature was investigated. Lowering the reaction temperature to 4 or -20 °C, or increasing to 50 °C, the enantioselectivity was worse than at room temperature. Afterward, different concentrations (entry 13 and 14) were tested without any improvement in the enantiomeric excess. Finally, different catalyst loadings were evaluated (entries 15-17), obtaining an enhancement of the enantiomeric excess to 67% ee and 46% yield, when 2 mol% of catalyst was used (entry 16). Our efforts to improve the enantiomeric excess of compound **3a** were unsuccessful; therefore, we decided to study the scope and generality of the reaction with the conditions shown in entry 16, Table 2.

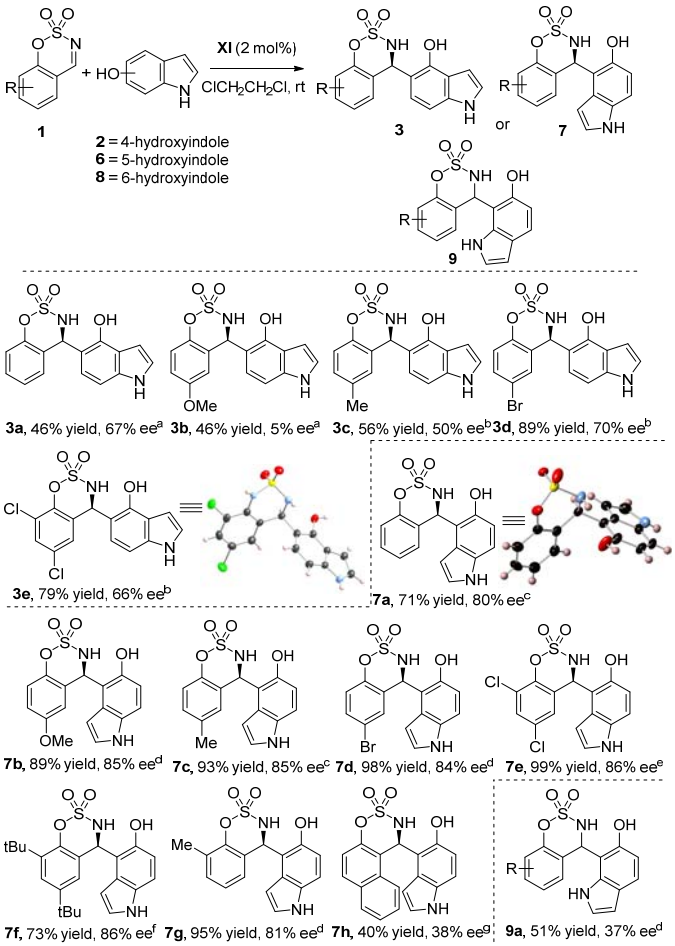
Table 2 Optimization of the reaction conditions.[a]



Entry	Solvent	T (º C)	t (h)	**3a** Yield (%)[b]	**3a** ee (%)[c]	**4a** Yield (%)[d]	**5a** Yield (%)[d,e]
1	CH_2Cl_2	20	6	48	43	15	24
2	$CHCl_3$	20	5	36	41	n.d.	n.d.
3	$ClCH_2CH_2Cl$	20	5	53	57	13	22
4	toluene	20	18	29	17	18	23
5	Et_2O	20	18	52	8	12	10
6	THF	20	24	24	10	8	5
7	EtOAc	20	24	41	11	12	8
8	CH_3CN	20	24	27	32	8	10
9	MeOH	20	24	25	22	22	17
10	$ClCH_2CH_2Cl$	-20	24	43	49	17	28
11	$ClCH_2CH_2Cl$	4	5	53	54	13	20
12	$ClCH_2CH_2Cl$	50	6	57	45	14	19
13[f]	$ClCH_2CH_2Cl$	20	2	50	43	16	22
14[g]	$ClCH_2CH_2Cl$	20	6	61	35	15	13
15[h]	$ClCH_2CH_2Cl$	20	4	53	53	15	27
16[i]	$ClCH_2CH_2Cl$	20	6	46	67	14	22
17[j]	$ClCH_2CH_2Cl$	20	6	56	41	20	23

[a] Reaction conditions: **1a** (0.1 mmol), **2a** (0.2 mmol) and **XI** (5 mol%) in 1 mL of solvent. [b] Isolated yield after column chromatography. [c] Determined by chiral HPLC. [d] Determined by ^{1}H NMR. [e] The dr of compound **5a** was around 1:1 in all cases by ^{1}H NMR. [f] The reaction was performed in 0.35 mL of solvent. [g] The reaction was performed in 3 mL of solvent. [h] 10 mol% of catalyst was used. [i] 2 mol% of catalyst was used. [j] 0.5 mol% of catalyst was used.

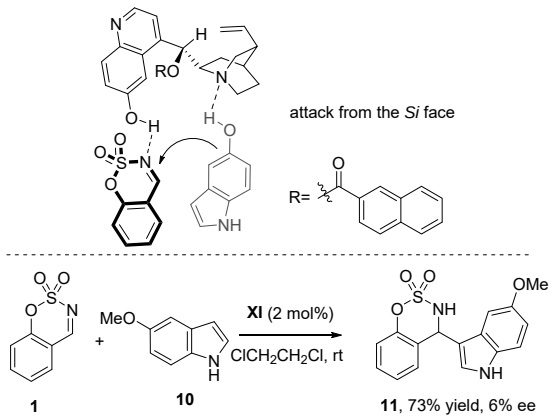
First we studied, the effect of the substituents in the cyclic imines using 4-hydroxyindole as nucleophile (Scheme 2). The presence of a strong electron-donating group (MeO) at 6 position led to a nearly racemic mixture. While the presence of electron-withdrawing groups at 6 position (Br), led to an improvement of the yield of product **3d** to 89%[16] maintaining the enantioselectivity (70% ee). Once that we studied the reaction with 4-hydroxyindole, we decided to apply our methodology for the functionalization of indoles in every position of the carbocyclic ring. So, we continued our research studying the reaction of 5-hydroxyindole (**6**) and differently substituted benzoxathiazines 2,2-dioxides. To our delight, the corresponding product **7a**, regioselectively alkylated at 4 position, was obtained with good yield (71%)[17] and good enantiomeric excess (80% ee). Introduction of substituents in the aromatic ring of the cyclic imines revealed that both electron-donating and -withdrawing groups were well-tolerated at 6 position on the ring (**7b**–**7d**, 89-98% yield, 84–85%ee). Moreover, cyclic imines (**1e**–**1f**) with two substituents that provide steric hindrance, were suitable substrates for the aza-Friedel-Crafts reaction, affording good enantiomeric excess (86% ee) and good yields (99% and 73%). In addition, benzoxathiazines 2,2-dioxides bearing functional groups in the 8-position were also tolerated as substrate giving the reaction product 7g, with good yield (95%) and enantiomeric excess (81%). However, a naphthyl ring was not tolerated and the corresponding product was obtained with moderate yield and enantioselectivity.[18] Unfortunately, 6-hydroxyindole showed low reactivity under the optimized reaction conditions, the 7-alkylated product **9a** was obtained with complete regioselectivity, but moderate yield (51%) and low enantioselectivity (37% ee) after 3 days of reaction. Finally, 7-hydroxyindole was also tested under the optimized reaction conditions, but unfortunately the regioselectivity was low obtaining a ratio (1:1) of alkylated products at C-6 and at C-4, and the enantiomeric excess of these compounds were also very poor.[15] We attribute these results to an interference between the NH of the indole and the hydroxyl group.



Scheme 2. Scope of the enantioselective aza-Friedel-Crafts reaction of hydroxyindoles with cyclic imines. Reaction conditions: **1** (0.1 mmol), hyroxyindole (0.2 mmol) and **XI** (2 mol%) in 1 mL of $ClCH_2CH_2Cl$. Isolated yield after column chromatography. Determined by chiral HPLC. [a] 6 h reaction time. [b] 15 h reaction time. [c] 48 h reaction time. [d] 72 h reaction time. [e] 3 h reaction time. [f] 144 h reaction time. [g] 240 h reaction time.

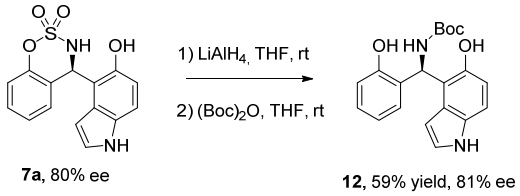
The absolute configuration of compounds **3e** and **7a** was determined to be (*R*) by X-ray analysis[19] (Scheme 2), and for the rest of the products **3** and **7** was assigned on the assumption of a uniform mechanistic pathway. The observed stereochemistry can be explained though a plausible transition state depicted in the Scheme 3, where the catalyst is activating both the nucleophile and the electrophile through hydrogen bonding. The hydrogen bonding between the quinuclidine tertiary amine and the hydroxyl group of indole can be ascertained due to the different reactivity of 5-methoxyindole (**10**). When **10** was used

as nucleophile under the optimized reaction conditions, the reaction took place at the C-3 position of the indole (the normal position for a Friedel-Crafts alkylation) and the corresponding product **11** was obtained with good yield (73%), but nearly racemic (6% ee).



Scheme 3. Elucidation of bifunctional mode of activation.

Finally, we carried out the reduction of the sulfamidate moiety[20] of compound **7a** (Scheme 4), using $LiAlH_4$ obtaining the corresponding chiral amine bearing a phenol and hydroxyindole moieties, which was protected *in situ* as its Boc derivative **12**, with good yield (59%) and preserving the enantiomeric excess of compound **7a** (81% ee).



Scheme 4. Synthetic transformation.

Conclusions

In summary, we have developed an enantioselective functionalization in the carbocyclic ring of indoles through an aza-Friedel-Crafts alkylation of hydroxyindoles with benzoxathiazines 2,2-dioxides as electrophiles using a quinine-derived bifunctional organocatalyst. The corresponding chiral sulfamidates were obtained with good yields and from moderate to good enantioselectivities. In general, the best yields and enantioselectivities are obtained when 5-hydroxyindole is used as nucleophile the reaction occurring at the C-4 position of the carbocyclic ring. This methodology represents the first Friedel-Crafts alkylation in the carbocyclic ring of indoles with cyclic imines.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

‡ Footnotes relating to the main text should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

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15 See supporting information for further details.

16 We did not observed the formation of the 7-alkylated product **4d** or the 5,7-dialkylated product **5d**.

17 We only observed the product alkylated at C-4 position, we did not observed in the crude ^{1}H NMR any other alkylated product.

18 Cyclic ketimines such as 4-methylbenzo[*e*][1,2,3]oxathiazine 2,2-dioxide or 3-methylbenzo[*d*]isothiazole 1,1-dioxide were not reactive under the optimized reaction conditions.

19 CCDC 1875758 (**3e**) and CCDC 1846586 (**7a**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

20 L. De Munck, A. Monleón, C. Vila and J. R. Pedro, *Adv. Synth. Catal*. 2017, **359**, 1582.