Organocatalytic Asymmetric Addition of Naphthols to Isatin-derived Ketimines: Highly Enantioselective Construction of Tetrasubstituted Stereocenters

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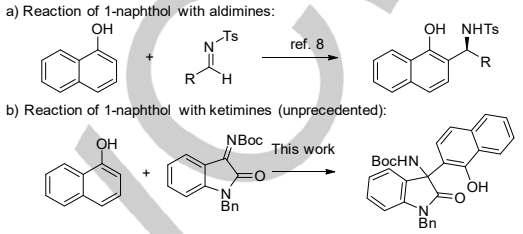
Abstract: A highly enantioselective addition of naphthols and activated phenols to ketimines derived from isatines has been achieved using a quinine-derived thiourea organocatalyst. The reaction affords chiral 3-amino-2-oxindoles with a quaternary stereocenter in high yields (up to 99%) and excellent enantioselectivities (up to 99%). This methodology represents, to the best of our knowledge, the first highly enantioselective addition of naphthols to ketimines.

The development of mild, effective, catalytic and enantioselective reactions for C-C bond formation is a fundamental topic in modern organic chemistry. In this context, the enantioselective addition of nucleophiles to imines provides a straightforward methodology for the formation of chiral amines.[1] These are valuable compounds in organic synthesis, and tremendous efforts have been made in order to establish efficient methodologies for their synthesis.[2] In particular, the asymmetric aza-Friedel-Crafts reaction represents one of the most powerful strategies for the synthesis of chiral benzylic amines.[3] Despite the great achievements in the enantioselective aza-Friedel-Crafts reaction with aldimines,[4] the corresponding asymmetric reaction using ketimines has been proved to be more challenging.[5] Moreover, while the major efforts have been focused in the use of indoles and pyrroles as nucleophiles,[3] the application of arenes in the F-C reaction is trickier, as a result of their reduced nucleophilicity and, consequently, there is an urgent requirement to develop novel asymmetric F-C reactions employing these partners. For example, naphthols are F-C donors that have been used with a range of electrophiles, such azodicarboxilates[6] or activated olefins.[7] In the case of aza-Friedel-Crafts, naphthols have been used as nucleophiles for the asymmetric addition to aldimines.[8] However, to the best of our knowledge, the enantioselective aza-F-C reaction of naphthols with ketimines remains elusive and has not been reported to date (Scheme 1). Moreover, chiral aminonaphthols are important compounds with biological activities [9] and can be used as chiral ligands in asymmetric synthesis.[10]



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

In the other hand, the oxindole skeleton bearing a tetra-substituted stereogenic center at the 3-position is a privileged heterocyclic structure present in many biologically active natural products and pharmaceutical drugs.[11] Among these compounds, 3-substituted 3-amino-2-oxindole has been found as a crucial structure present in molecules with pharmaceutical properties such SSR149415,[12] AG-041R[13] or NITD609[14] (Figure 1). Two methodologies have been established for the straightforward synthesis of chiral 3-substituted 3-amino-2-oxindole,[15] one is the electrophilic amination of oxindoles,[16] and the other is the addition of nucleophiles to isatin-derived ketimines. Recently, several catalytic enantioselective additions to these ketimines have been reported, including Mannich reactions,[17] Strecker reactions,[18] aza-Henry reactions,[19] and other asymmetric reactions[20] including aza-Friedel-Crafts.[5f] Although, the enantioselective addition of naphthols to isatin-derived ketimines has not been reported yet. As a part of our ongoing interest in the asymmetric synthesis of chiral tetrasubstituted centers through an enantioselective Friedel-Crafts reaction,[21] herein we present the first enantioselective addition of naphthols to isatin-derived ketimines catalyzed by a bifunctional organocatalyst.

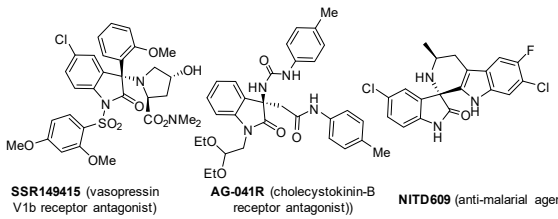


Figure 1. Examples of biologically active 3-substituted 3-amino-2-oxindoles.

Initially, the reaction of 1-naphthol **1a** with isatin-derived *N*-Boc ketimine **2a** was chosen as a model reaction to screen various chiral bifunctional organocatalysts bearing a tertiary amine moiety, which have been widely used to activate both electrophile and nucleophile.[22],[23] Quinine (**I**) could catalyzed

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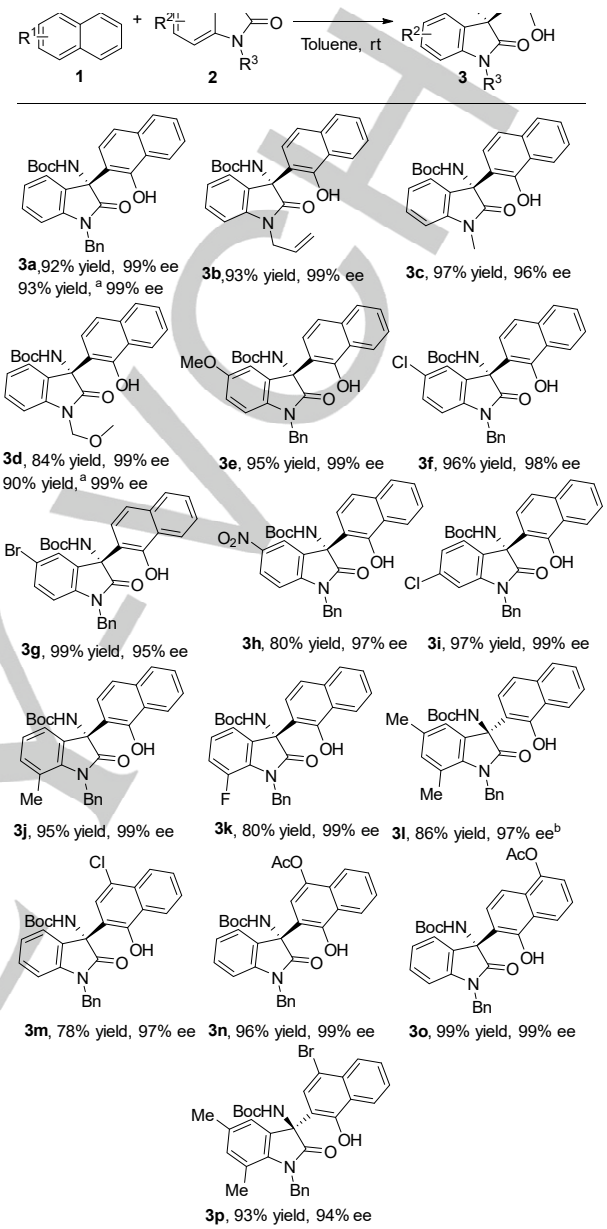
the reaction to obtain the product **3a**, although nearly racemic after 3 days (Table 1, entry 1). Catalyst **II** showed better enantioselectivity (45% *ee*), with a moderate yield (Table 1, entry 2). To our delight, when quinine-derived thiourea[24] **III** was used (Table 1, entry 3), the reaction proceed smoothly with excellent results. The chiral amine **3a** was obtained with 95% yield and 99% *ee*, after 7 hours. Other thiourea organocatalyst bearing a tertiary amine moiety, such as Takemoto's catalyst **IV**, proved to be an efficient catalyst in terms of enantioselectivity (96% *ee*), though with a decreased yield after 24 h (Table 1, entry 4). Other solvents were also screened, but a drop in the reactivity was observed, especially when using THF (entries 5 and 6). The aza-Friedel-Crafts product **3a** could be also achieved when only 2 or 1 mol% of catalyst was used (entry 7 and 8, respectively), although with 1 mol% the enantiomeric excess was slightly lower (96% ee). Furthermore, the opposite enantiomer of **3a**, was achieved with excellent enantioselectivity (-99% ee, entry 9), when quinidine-derived thiourea **V** (2 mol%) was used as a catalyst.

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

Entry	Catalyst (mol%)	Solvent	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**I** (5 mol%)	Toluene	72	60	2
2	**II** (5 mol%)	Toluene	24	41	45
3	**III** (5 mol%)	Toluene	7	95	99
4	**IV** (5 mol%)	Toluene	24	78	96
5	**III** (5 mol%)	DCM	13	84	99
6	**III** (5 mol%)	THF	24	20	92
7	**III** (2 mol%)	Toluene	7	92	99
8	**III** (1 mol%)	Toluene	15	94	96
9	**V** (2 mol%)	Toluene	13	94	-99[d]

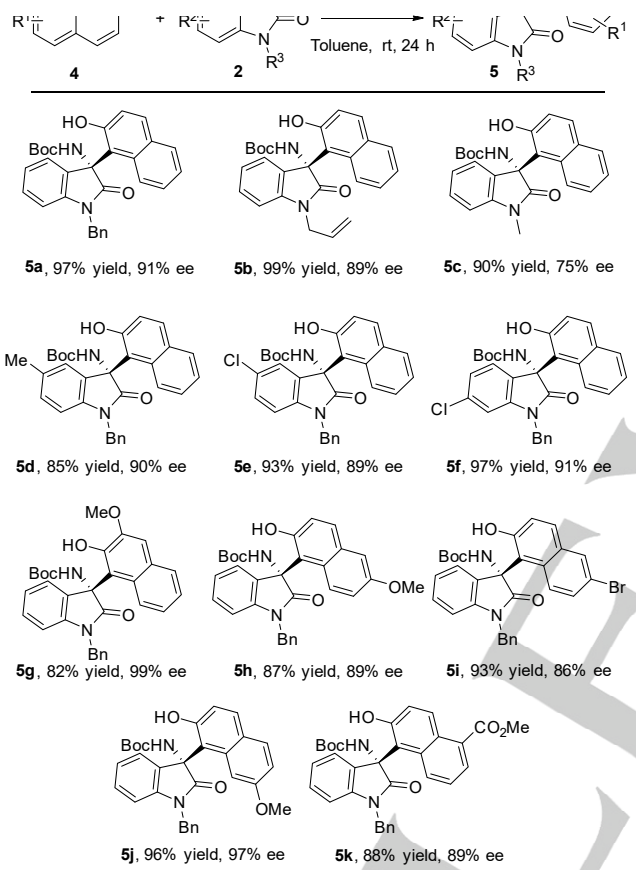
[a] Reaction conditions: 0.1 mmol **1a**, 0.1 mmol **2a**, and catalyst in dry solvent (1.5 mL) at rt. [b] Isolated yield after column chromatography. [c] Enantiomeric excess determined by chiral HPLC. [d] Opposite enantiomer.



Scheme 2. Scope of the aza-Friedel-Crafts reaction of **1** with **2**. Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol), and catalyst **III** (2 mol%) in dry toluene (1.5 mL) at rt for 12 h. [a] 1 mmol scale reaction. [b] Catalyst **V** (2 mol%) was used.

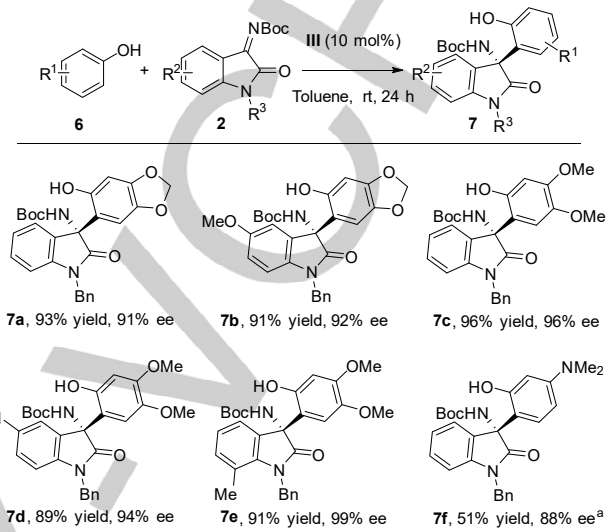
Based on the above screening conditions, the substrate scope was investigated under the optimal conditions to run the aza-Friedel-Crafts reaction in toluene at room temperature, using 2 mol% of catalyst **III** (Scheme 2). First of all, we studied the effect of the substituent group at the 1-position of the ketimine **2**. The isatin-derived ketimines with alkyl substituents at the nitrogen (R^3 = Bn, allyl, Me or MOM) were efficiently transformed to the corresponding products preserving the excellent enantioselectivity (96-99% ee).[25] Subsequently, we evaluated different *N*-Boc ketimines derived from various

substituted *N*-benzylisatines. We were delighted to obtain the corresponding products **3** with high yields and excellent enantioselectivities (95-99% ee), independently of the electronic character and the position of the substituents of the aromatic ring of the isatin. Finally, different substituted 1-naphthols were tested affording the corresponding products (**3m-3o**) with excellent results (97-99% ee). Furthemore, 1 mmol scale reactions were carried out for compounds **3a** and **3d**, obtaining similar results to the 0.1 mmol scale reactions.



Scheme 3. Scope of the aza-Friedel-Crafts reaction of **4** with ketimines **2**. Reaction conditions: **4** (0.1 mmol), **2** (0.1 mmol), and catalyst **III** (10 mol%) in dry toluene (1.5 mL) at rt for 24 h.

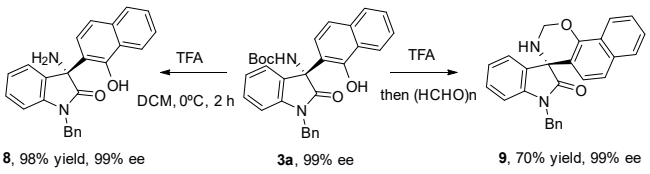
Once we studied the aza-Friedel-Crafts reaction with several 1-naphthols (**1**), we focused our attention on the reaction of isatin-derived ketimines **2** with different substituted 2-naphthols (**4**). Remarkably, 2-naphthol was found to be less reactive under the optimized reaction conditions, and 10 mol% of catalyst were used to obtain satisfactory results. Oxindole **5a**, was obtained with 97% yield and 91% *ee*, after 24 h. Various substituted ketimines were reacted providing the corresponding product (**5b-5f**) with great yields (85-99%) and high enantioselectivities (75-91% ee). Next, we studied the influence of susbtituents in the naphthol **4** when reacts with **2a**. For this purpose, assorted 2-naphthols substituted with electron-donating or electron-withdrawing groups were tested, providing good results in most of the cases. Remarkably, when 3-MeO-2-naphthol was used as a nucleophile, an excellent enantioselectivity of 99% was achieved. The absolute configuration of product **3p** and **5i** was ascertained as (*R*) on the basis of an X-ray crystal analysis.[26]



Scheme 4. Scope of the aza-Friedel-Crafts reaction of **6** with ketimines **2**. Reaction conditions: **6** (0.1 mmol), **2** (0.1 mmol), and catalyst **III** (10 mol%) in dry toluene (1.5 mL) at rt for 24 h.[a] The reaction was run for 36 h.

Interestingly, our method could also be applied to sesamol and other activated phenols (**6**), obtaining the corresponding derivatives **7** with good yields and high enantioselectivities (Scheme 4). The amino-methyl-sesamol framework is present in many commercially exploited drugs, but up to now, just the enantioselective addition to aldimines has been reported.[27] Sesamol derivatives **7a** and **7b**, could be obtained with 91 and 92% ee, respectively. While with 2,3-dimethoxyphenol, the corresponding substituted oxindoles **7c-7e**, were achieved with higher enantioselectivity (94-99% ee). Moreover, 3-(dimethylamino)phenol[28] was found to be less reactive, and the corresponding product **7f** was gained with lower yield (51%), although with good enantiomeric excess (88%).

Finally, the removal of the Boc group was achieved in **3a** by using trifluoroacetic acid (TFA) in DCM at 0 ºC affording the free amine **8** in 98% yield without loss of the stereochemical purity (Scheme 5). Furthermore, the spyrocicle **9** was obtained in a 70% yield by treatment of oxindole **3a** with TFA followed by addition of paraformaldehyde in a one pot procedure.



Scheme 5. Transformations of product **3a**.

In summary, a highly enantioselective addition of naphthols to isatin-derived ketimines is presented. In the presence of the quinine-derived thiourea **III**, the corresponding chiral 3-substituted 3-amino-2-oxindoles were obtained in excellent yields (up to 99%) and high enantioselectivities (up to 99% *ee*). Features of this methodology include the wide substrate scope, high yields, excellent enantioselectivities and mild conditions. The present study represents the first highly enantioselctive aza-Friedel-Crafts reaction of naphthols and activated phenols with ketimines.[29]

Acknowledgements

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Keywords: asymmetric synthesis • Friedel-Crafts • isatin-derived ketimines • naphthol • organocatalysis

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[26] See supporting information for further details. CCDC 1048104 (**3p**) and 1048103 (**5i**) contain 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.

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[29] There is one example of the addition of **4a** to **2a**, in the ref. 8c, although the enantiomeric excess is low (43% ee).

Entry for the Table of Contents (Please choose one layout)

Layout 2:

COMMUNICATION

*Marc Montesinos-Magraner, Carlos Vila, Rubén Cantón, Gonzalo Blay, Isabel Fernández, M. Carmen Muñoz, José R. Pedro**

Organocatalytic Asymmetric Addition of Naphthols to Isatin-derived Ketimines: Highly Enantioselective Construction of Tetrasubstituted Stereocenters