

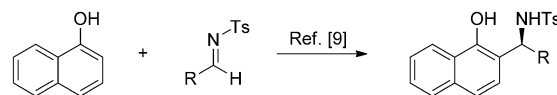
Organocatalytic Asymmetric Addition of Naphthols and Electron-Rich Phenols to Isatin-Derived Ketimines: Highly Enantioselective Construction of Tetrasubstituted Stereocenters**

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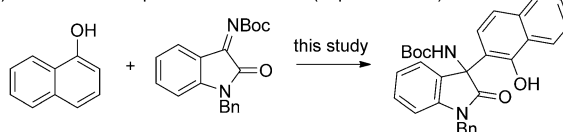
Abstract: A quinine-derived thiourea organocatalyst promoted the highly enantioselective addition of naphthols and activated phenols to ketimines derived from isatins. The reaction afforded chiral 3-amino-2-oxindoles with a quaternary stereocenter in high yields (up to 99%) with excellent enantioselectivity (up to 99% ee). To the best of our knowledge, this transformation is 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 route to chiral amines.^[1] Tremendous effort has been devoted to establishing efficient methodologies for the synthesis of these valuable compounds in organic synthesis.^[2] In particular, the asymmetric aza-Friedel–Crafts reaction is one of the most powerful strategies for the synthesis of chiral benzylic amines.^[3] Despite great achievements in the enantioselective aza-Friedel–Crafts reaction of aldimines,^[4] the corresponding asymmetric reaction of ketimines has proved to be more challenging.^[5] Moreover, the main focus has been on the use of indoles and pyrroles as nucleophiles.^[3] The application of arenes in the Friedel–Crafts reaction is trickier as a result of their reduced nucleophilicity. Consequently, there is an urgent requirement to develop novel asymmetric Friedel–Crafts reactions with these substrates. Naphthols are Friedel–Crafts donors that have been used with a range of electrophiles, such as azodicarboxylates,^[6] ketones,^[7] and activated alkenes.^[8] In the case of aza-

a) Reaction of 1-naphthol with aldimines:



b) Reaction of 1-naphthol with ketimines (unprecedented):



Scheme 1. Enantioselective aza-Friedel–Crafts reaction of 1-naphthol with imines. Boc = *tert*-butoxycarbonyl, Bn = benzyl, Ts = *p*-toluenesulfonyl.

Friedel–Crafts reactions, naphthols have been used as nucleophiles for asymmetric addition to aldimines.^[9] However, to the best of our knowledge, the enantioselective aza-Friedel–Crafts reaction of naphthols with ketimines remains elusive and has not been reported to date (Scheme 1). The products of such a reaction, chiral aminonaphthols, are important biologically active compounds^[10] that can also be used as chiral ligands in asymmetric synthesis.^[11]

The oxindole skeleton with a tetrasubstituted stereogenic center at the 3-position is a privileged heterocyclic structure present in many biologically active natural products and pharmaceutical drugs.^[12] The 3-substituted 3-amino-2-oxindole motif is a crucial structure present in a number of molecules with pharmaceutical properties, such as SSR149415,^[13] AG-041R,^[14] and NITD609^[15] (Scheme 2). Two methods have been established for the straightforward synthesis of chiral 3-substituted 3-amino-2-oxindoles:^[16] the electrophilic amination of oxindoles,^[17] and the addition of nucleophiles to isatin-derived ketimines. Recently, several examples of catalytic enantioselective addition to these ketimines have been reported, including Mannich reactions,^[18] Strecker reactions,^[19] aza-Henry reactions,^[20] and other asymmetric reactions,^[21] including the aza-Friedel–Crafts reaction.^[5f] However, the enantioselective addition of naphthols to isatin-derived ketimines has not been reported previously. As a part of our ongoing interest in the asymmetric construction of tetrasubstituted centers through enantioselective Friedel–Crafts reactions,^[22] we present herein the enantioselective addition of naphthols to isatin-derived ketimines in the presence of a bifunctional organocatalyst.

Initially, we chose the reaction of 1-naphthol (**1a**) with the isatin-derived *N*-Boc-protected ketimine **2a** as a model reaction to screen various chiral bifunctional organocatalysts

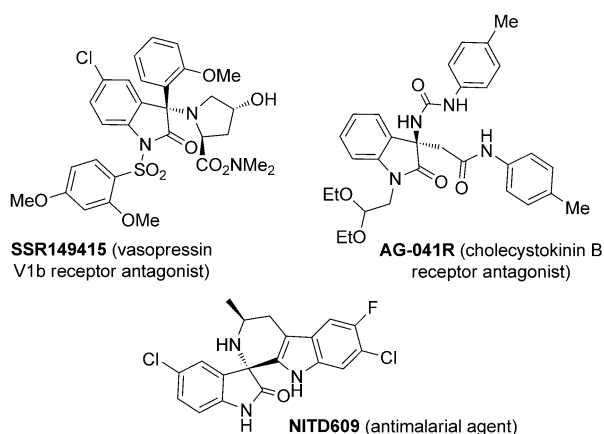
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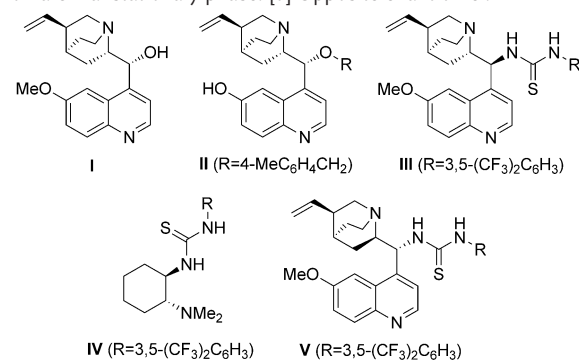
Scheme 2. Examples of biologically active 3-substituted 3-amino-2-oxindoles.

containing a tertiary-amine moiety; such groups have been widely used to activate both an electrophile and a nucleophile.^[23,24] Quinine (**I**) catalyzed the reaction to give product **3a**, although nearly racemic, in 60% yield after 3 days (Table 1, entry 1). Catalyst **II** showed better enantioselectivity (45% *ee*) and moderate reactivity (Table 1, entry 2). To our delight, when the quinine-derived thiourea^[25] **III** was used

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

Entry	Catalyst	Solvent	<i>t</i> [h]	Yield [%] ^[b]	<i>ee</i> [%] ^[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 %)	CH ₂ Cl ₂	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: **1a** (0.1 mmol), **2a** (0.1 mmol), catalyst, dry solvent (1.5 mL), room temperature. [b] Yield of the isolated product after column chromatography. [c] The *ee* value was determined by HPLC on a chiral stationary phase. [d] Opposite enantiomer.

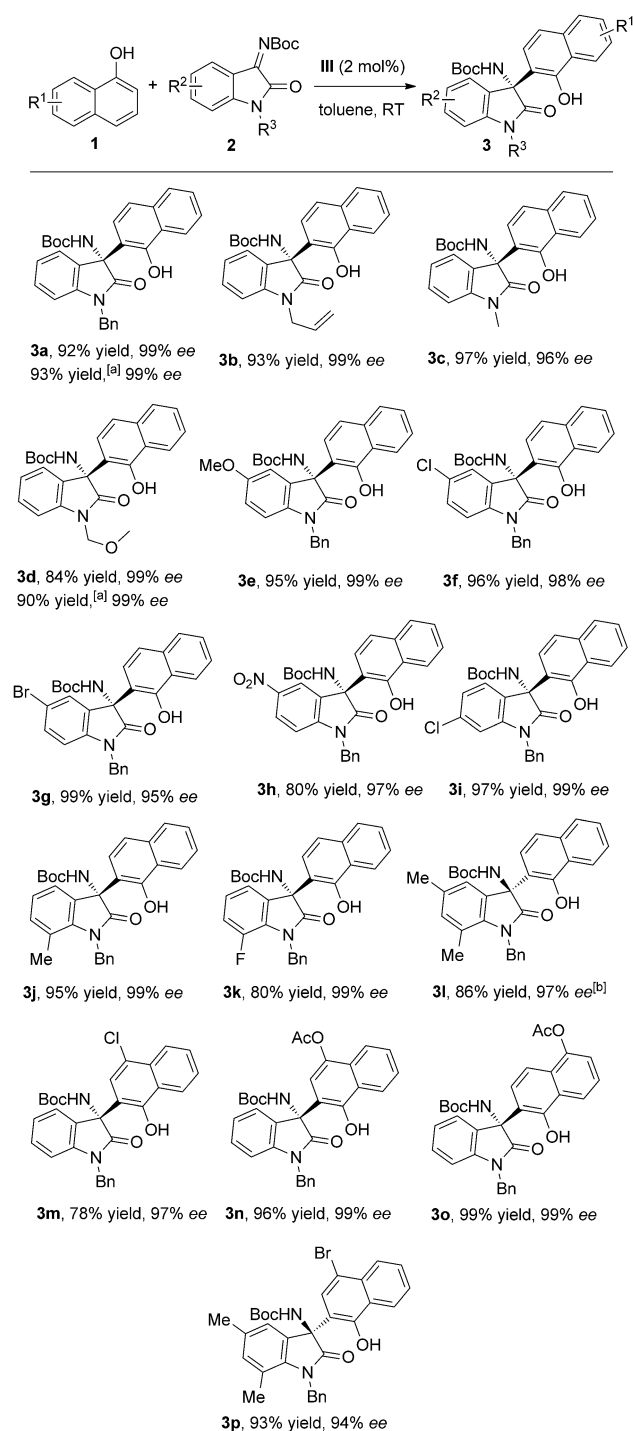


(Table 1, entry 3), the reaction proceeded smoothly with excellent results: The chiral amine **3a** was obtained in 95% yield and with 99% *ee* after 7 h. Other thiourea organo-catalysts containing a tertiary-amine moiety, such as the Takemoto catalyst **IV**, proved to be efficient in terms of enantioselectivity, but a lower yield was observed after 24 h (Table 1, entry 4). A drop in reactivity was observed with other solvents, especially in the case of THF (Table 1, entries 5 and 6). The aza-Friedel–Crafts product **3a** was also obtained when the catalyst loading was decreased to only 2 or 1 mol % (Table 1, entries 7 and 8), although with 1 mol % of the catalyst the *ee* value was slightly lower (96%). Furthermore, the opposite enantiomer of **3a** was formed with excellent enantioselectivity (−99% *ee*) when the quinidine-derived thiourea **V** (2 mol %) was used as the catalyst (Table 1, entry 9).

The scope of the aza-Friedel–Crafts reaction was investigated under the optimal conditions with catalyst **III** (2 mol %; Scheme 3). First of all, we studied the effect of the substituent group at the 1-position of the ketimine **2**. Isatin-derived ketimines with alkyl substituents at this nitrogen atom (R³=Bn, allyl, Me, or methoxymethyl) were efficiently transformed into the corresponding products with excellent enantioselectivity (96–99% *ee*).^[26] Subsequently, we evaluated *N*-Boc-protected ketimines derived from various substituted *N*-benzylisatins and obtained the corresponding products **3** in high yields with high enantioselectivity (95–99% *ee*), regardless of the electronic character of the aromatic ring of the isatin and the position of the substituent. The use of different substituted 1-naphthols also afforded the expected products **3m–o** with excellent results (97–99% *ee*). Furthermore, reactions of compounds **3a** and **3d** on a 1 mmol scale gave similar results to the reactions carried out on a 0.1 mmol scale.

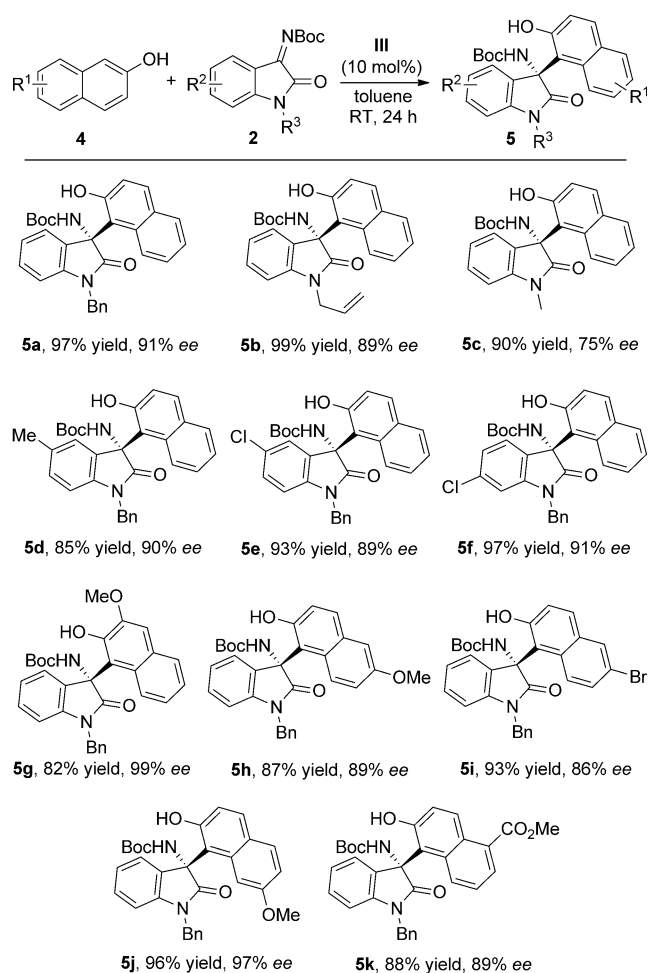
We next focused our attention on the aza-Friedel–Crafts reaction of isatin-derived ketimines **2** with substituted 2-naphthols **4** (Scheme 4). Remarkably, 2-naphthol was found to be less reactive than 1-naphthol, and a catalyst loading of 10 mol % was required for satisfactory results. Oxindole **5a** was obtained in 97% yield with 91% *ee* after 24 h. Various substituted ketimines underwent this reaction with 2-naphthol to give the corresponding products **5b–f** in high yield with 75–91% *ee*. Next, we studied the influence of substituents in the naphthol **4** on its reaction with **2a**. Assorted 2-naphthols substituted with an electron-donating or electron-withdrawing group provided good results in most cases. Remarkably, when 3-methoxy-substituted 2-naphthol was used as the nucleophile, product **5g** was obtained with 99% *ee*. The absolute configuration of products **3p** and **5i** was ascertained as *R* on the basis of X-ray crystal analysis.^[27]

Our method could also be applied to the use of sesamol and other activated phenols **6** as the nucleophile. The corresponding products **7** were obtained in good yield with high enantioselectivity (Scheme 5). The amino-methyl-sesamol framework is present in many commercially exploited drugs, but up to now, only the enantioselective addition of sesamol to aldimines has been reported.^[28] Sesamol derivatives **7a** and **7b** were obtained with 91 and 92% *ee*, respectively. With 2,3-dimethoxyphenol, the corresponding



Scheme 3. Scope of the aza-Friedel–Crafts reaction of 1-naphthols **1** with ketimines **2**. Reaction conditions: **1** (0.1 mmol), **2** (0.1 mmol), catalyst **III** (2 mol%), dry toluene (1.5 mL), room temperature, 12 h. [a] The reaction was carried out on a 1 mmol scale. [b] Catalyst **V** (2 mol%) was used.

substituted oxindoles **7c–e** were formed with higher enantioselectivity (94–99% *ee*). However, 3-(dimethylamino)phenol^[29] was found to be less reactive, and the corresponding product **7f** was obtained in lower yield (51%), although with a good *ee* value of 88%.

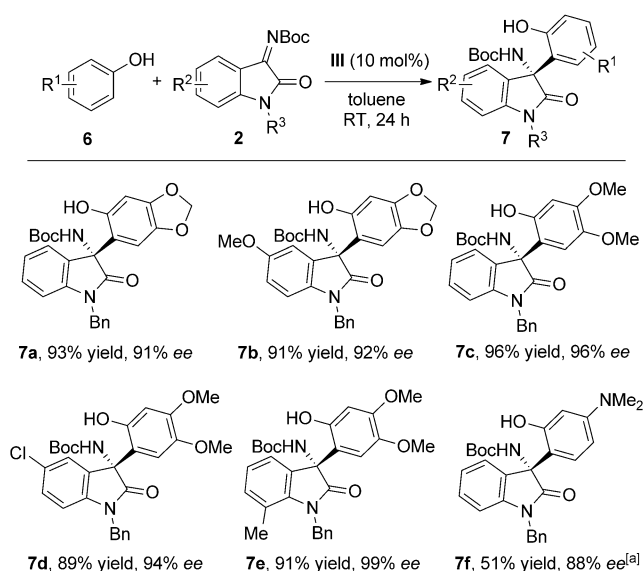


Scheme 4. Scope of the aza-Friedel–Crafts reaction of 2-naphthols **4** with ketimines **2**. Reaction conditions: **4** (0.1 mmol), **2** (0.1 mmol), catalyst **III** (10 mol%), dry toluene (1.5 mL), room temperature, 24 h.

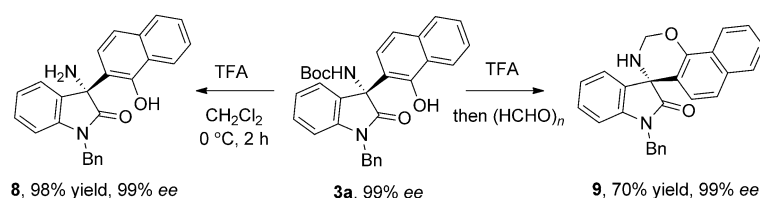
Finally, the Boc group in **3a** was removed with trifluoroacetic acid (TFA) in CH_2Cl_2 at 0°C to afford the free amine **8** in 98% yield without loss of stereochemical purity (Scheme 6). Furthermore, the spirocycle **9** was obtained in 70% yield by the treatment of oxindole **3a** with TFA and the subsequent addition of paraformaldehyde in a one-pot procedure.

In summary, we have presented a highly enantioselective addition of naphthols to isatin-derived ketimines. In the presence of the quinine-derived thiourea catalyst **III**, the corresponding chiral 3-substituted 3-amino-2-oxindoles were obtained in excellent yield (up to 99%) with high enantioselectivity (up to 99% *ee*). Important features of this methodology include its wide scope with respect to the variety of applicable substrates and the mild reaction conditions. This transformation is the first highly enantioselective aza-Friedel–Crafts reaction of naphthols and activated phenols with ketimines.^[30]

Keywords: asymmetric synthesis · Friedel–Crafts reactions · isatin-derived ketimines · naphthols · organocatalysis



Scheme 5. Scope of the aza-Friedel-Crafts reaction of phenols **6** with ketimines **2**. Reaction conditions: **6** (0.1 mmol), **2** (0.1 mmol), catalyst **III** (10 mol%), dry toluene (1.5 mL), room temperature, 24 h. [a] The reaction was carried out for 36 h.



Scheme 6. Transformations of product **3a**.

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