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

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

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.10 These are valuable compounds in organic synthesis, and tremendous efforts have been made in order to establish efficient methodologies for their synthesis.5f In particular, the asymmetric aza-Friedel-Crafts reaction represents one of the most powerful strategies for the synthesis of chiral benzyl amines.11 Despite the great achievements in the enantioselective aza-Friedel-Crafts reaction with aldimes,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,5 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 as azodicarboxilates6 or activated olefins.5i In the case of aza-Friedel-Crafts, naphthols have been used as nucleophiles for the asymmetric addition to aldimes.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 activities9 and can be used as chiral ligands in asymmetric synthesis.10

The development of novel asymmetric organocatalytic reactions for the construction of chiral tetrasubstituted centers has been an area of great interest in modern organic chemistry. In this context, the enantioselective addition of nucleophiles to imines provides a straightforward methodology for the formation of chiral amines.10 These are valuable compounds in organic synthesis, and tremendous efforts have been made in order to establish efficient methodologies for their synthesis.5f In particular, the asymmetric aza-Friedel-Crafts reaction represents one of the most powerful strategies for the synthesis of chiral benzyl amines.11 Despite the great achievements in the enantioselective aza-Friedel-Crafts reaction with aldimes,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,5 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 as azodicarboxilates6 or activated olefins.5i In the case of aza-Friedel-Crafts, naphthols have been used as nucleophiles for the asymmetric addition to aldimes.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 activities9 and can be used as chiral ligands in asymmetric synthesis.10

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In the other hand, the oxindole skeleton bearing a tetrasubstituted stereoogenic 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-041R13 or NITD60914 (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 reactions20 including aza-Friedel-Crafts.9 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.

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

![Scheme 1. Enantioselective aza-Friedel-Crafts reaction of 1-naphthol with imines.](image-url)

![Figure 1. Examples of biologically active 3-substituted 3-amino-2-oxindoles.](image-url)
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 III was used (Table 1, entry 3), the reaction proceeded 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.*

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst (mol%)</th>
<th>Solvent</th>
<th>Time (h)</th>
<th>Yield (%)</th>
<th>Ee (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>I (5 mol%)</td>
<td>Toluene</td>
<td>72</td>
<td>60</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>II (5 mol%)</td>
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<td>45</td>
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<tr>
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<td>III (5 mol%)</td>
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<td>78</td>
<td>96</td>
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<tr>
<td>5</td>
<td>III (5 mol%)</td>
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<td>99</td>
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<tr>
<td>6</td>
<td>III (5 mol%)</td>
<td>THF</td>
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<td>92</td>
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<tr>
<td>7</td>
<td>III (2 mol%)</td>
<td>Toluene</td>
<td>7</td>
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<tr>
<td>8</td>
<td>III (1 mol%)</td>
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<td>94</td>
<td>96</td>
</tr>
<tr>
<td>9</td>
<td>V (2 mol%)</td>
<td>Toluene</td>
<td>13</td>
<td>94</td>
<td>-99d</td>
</tr>
</tbody>
</table>

[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.

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 (R3 = Bn, allyl, Me or MOM) were efficiently transformed to the corresponding products preserving the excellent enantioselectivity (96-99% ee). Subsequently, we evaluated different N-Boc ketimines derived from various...
substituted N-benzylisatins. 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). Furthermore, 1 mmol scale reactions were carried out for compounds 3a and 3d, obtaining similar results to the 0.1 mmol scale reactions.

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. 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 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 °C affording the free amine 8 in 98% yield without loss of the stereochromic purity (Scheme 5). Furthermore, the spirocycle 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 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.

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. The reaction was run for 36 h.

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 enantioselectiveaza-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


The N1-unprotected isatin showed lower reactivity and the corresponding product was obtained with moderate yield (56%) and low ee (11%).

[25] See supporting information for further details. CCDC 1048104 (3p) and 1048103 (3q) 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.


[27] There is one example in the literature of the addition of 3-(dimethylamino)phenol to a cyclic ketimine, in the ref. 5c, although the enantiomeric excess is low (43% ee).

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

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