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Organocatalytic asymmetric Friedel–Crafts reaction of 1-naphthols with isatins: an enantioselective synthesis of 3-aryl-3-hydroxy-2-oxindoles

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ABSTRACT

An organocatalytic enantioselective Friedel–Crafts reaction of 1-naphthols with isatins has been developed employing bifunctional thiourea–tertiary amine organocatalysts. A variety of isatin derivatives react well with 1-naphthols in the presence of *Cinchona* derived thiourea **1a** to provide biologically important chiral 3-aryl-3-hydroxy-2-oxindoles (**3a**–**zg**) in good yield (70–84%) and moderate to good enantioselectivity (37–83%).

The Friedel–Crafts reaction has undoubtedly been positioned as one of the most important carbon–carbon bond forming reactions for the synthesis of valuable building blocks of biologically active molecules.[1] Recently, organocatalytic enantioselective Friedel–Crafts alkylation reactions[2] have attracted much attention due to advantages associated with organocatalytic transformation and its significance for the synthesis of optically active aromatic compounds. Various electron rich aromatic compounds have been successfully applied in the Friedel–Crafts reaction with diverse electrophiles and their enantioselective variants have also been well studied using small organic molecules as catalysts.[2] But, most of the reports in this area are focused on relatively more reactive heteroarenes–indoles/pyrroles.[3] However, electron rich arenes–naphthols have been demonstrated to be good Friedel–Crafts donors, *albeit* with a limited range of electrophiles.[4] Jørgensen,[4a] Chen,[4b] and Wang[4h] presented the organocatalytic asymmetric Friedel–Crafts reaction of 2-naphthol with azodicarboxylates, nitroolefins, and α,β-unsaturated aldehydes, respectively. Our group[5] and Wang and co-workers[6] simultaneously reported the first organocatalytic enantioselective Friedel–Crafts reaction of naphthols with aldimines employing *Cinchona* alkaloids.

Recently, isatins have emerged as valuable electrophiles and have successfully been used in a variety of organocatalytic reactions.[7] The nucleophilic addition to C-3 carbon of isatins provides biologically relevant 3-substituted 3-hydroxy-2-oxindoles.[8] Among them, 3-aryl-3-hydroxy-2-oxindoles are a useful class of compounds found in several drug candidates.[9] A variety of metal catalyzed asymmetric methods[10] have been developed for their synthesis, but the organocatalytic asymmetric methods[11] are limited to the use of heteroarenes. The organocatalytic asymmetric Friedel–Crafts reaction of electron rich arenes to isatins has not been reported.[12]

As part of our ongoing program in exploring bifunctional *Cinchona* alkaloids as suitable catalysts for asymmetric Friedel–Crafts reactions of isatins[11a], we reasoned that enantioinduction can be achieved in the Friedel–Crafts reaction of 1-naphthols with isatins through synergistic activation by bifunctional thiourea–tertiary amine organocatalysts (Scheme 1). Herein, we report the *epi*CDT (**I**) catalyzed the Friedel–Crafts-type addition of 1-naphthols to isatins.[13]

Initially, the reaction of 2-naphthol with *N*-benzylisatin in tetrahydrofuran (THF) in the presence of 4 Å molecular sieves using *epi*CDT (**I**) as a catalyst was performed. Unfortunately, there was no product formation noted even after 48 h of the reaction time (Scheme 2, Eq. 1). So, we studied the Friedel–Crafts (F–C) reaction of 1-naphthol (**1a**) with *N*-benzylisatin (**2a**) employing *epi*CDT (**I**, 10 mol %) in THF in the presence of 4 Å molecular sieves (Scheme 2, Eq. 2). Interestingly, the product **3a** was isolated in 78% yield and 77% ee after 6 h of the reaction time (Table 1, entry 1). Encouraged by this result, the catalytic ability of other *Cinchona*

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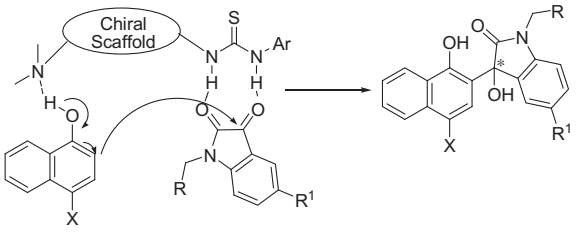
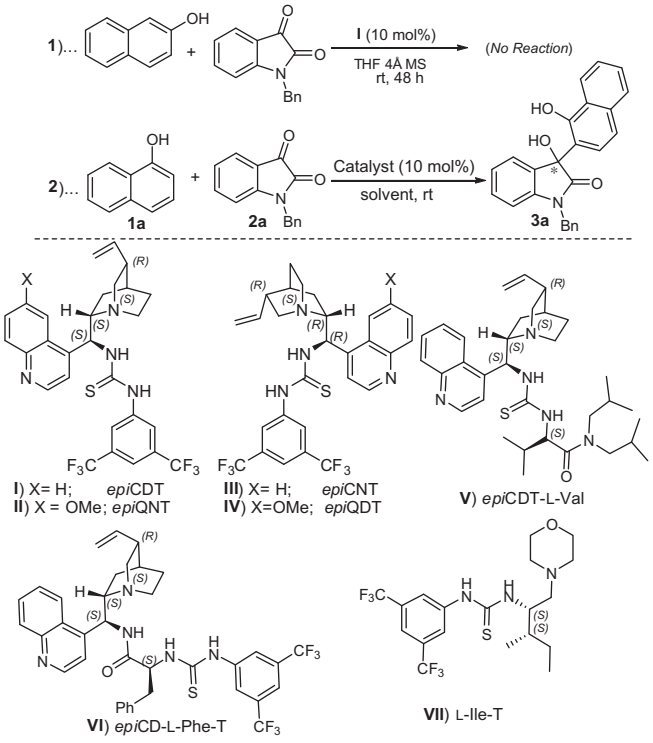


Scheme 1. Proposed dual activation for the thiourea–tertiary amine catalyzed, asymmetric Friedel–Crafts reaction of 1-naphthols with isatins.

alkaloids' derived thiourea derivatives (**II**–**VII**) was examined for the same reaction (Scheme 2, Eq. 2). The thiourea (**III**) prepared from cinchonine gave **3a** in 72% yield and 20% ee (Table 1, entry 3). The quinine and quinidine derived thiourea *epi*QNT (**II**) and *epi*QDT (**IV**) gave complementary enantiomers of adduct **3a** in good yield (71% and 69%), *albeit* with moderate enantioselectivity (68% ee and 40% ee) (Table 1, entries 2 and 4). The model reaction catalyzed by thiourea organocatalysts **V** and **VII** yielded **3a** in 46% and 67% yield; 40% ee and 11% ee, respectively (Table 1, entries 5 and 7). The organocatalysts **VI** having the thiourea group at a distance of six bonds from tertiary amine functionality yielded racemic adduct, indicating the importance of close proximity of tertiary amine and thiourea moiety for enantioselective reaction (Table 1, entry 6). The reaction catalyzed by *epi*CDT (**I**) at −18 °C took 13 h to provide **3a** in 68% yield and without any advantage in terms of enantioselectivity (Table 1, entry 8). Next, in order to identify the best solvent for this transformation, different solvents were screened employing *epi*CDT (**I**, 10 mol %) (Table 1, entries 9–15). The reaction performed in toluene, chloroform, and dichloromethane



Scheme 2. Bifunctional thiourea–tertiary amine catalyzed Friedel–Crafts reaction of naphthols with isatins.

Table 1
Optimization study[a]

Entry	Catalyst	Solvent	Time (h)	Yield[b] (%)	ee[c] (%)
1	**I**	THF	6	78	77 (+)
2	**II**	THF	6	71	68 (+)
3	**III**	THF	6	72	20 (+)
4	**IV**	THF	6	69	40 (−)
5	**V**	THF	8	46	40 (−)
6	**VI**	THF	8	40	0
7	**VII**	THF	8	67	11 (+)
8[d]	**I**	THF	13	68	76 (+)
9	**I**	Toluene	7	62	20 (+)
10	**I**	$CHCl_3$	6	78	52 (+)
11	**I**	DCM	6	76	56 (+)
12	**I**	MTBE	6	72	71 (+)
13	**I**	1,4-Dioxane	6	76	69 (+)
14	**I**	Diethyl ether	7	74	73 (+)
15	**I**	Ethyl acetate	6	79	71 (+)
16[e]	**I**	THF	6	75	56 (+)

[a] Reaction conditions: 0.1 mmol *N*-benzylisatin, 0.1 mmol of 1-naphthol, 4 Å molecular sieves (50 mg), and catalysts **I**–**VII** (10 mol %) in dry THF.
[b] Yield refers to isolated yield after column chromatography.
[c] Enantiomeric excess (ee) determined by chiral HPLC. The sign in parenthesis indicates enantiomers.
[d] Reaction was performed at −18 °C.
[e] 10 mol % of benzoic acid.

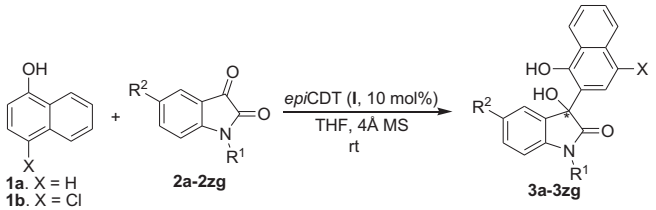
provided **3a** in 20% ee, 52% ee, and 56% ee, respectively (Table 1, entries 9–11). In etheral solvents such as methyl *tert*-butyl ether (MTBE), 1,4-dioxane, diethyl ether, the product **3a** was isolated in 72%, 76%, and 74% yield; 71% ee, 69% ee, and 73% ee, respectively (Table 1, entries 12–14). Further, the effect of benzoic acid as an additive on the Friedel–Crafts reaction was examined, which afforded **3a** in good yield but with lower enantioselectivity (Table 1, entry 16). Thus, the best optimized condition consists of 10 mol % of **I**, 4 Å molecular sieves, and THF as a solvent at ambient temperature providing Friedel–Crafts adduct **3a** in 78% yield and 77% ee; the optimized condition was used to study the substrate scope of this reaction.

Once armed with the optimized condition, the substrate scope was investigated by studying the Friedel–Crafts reaction of 1-naphthols (**1a**–**1b**) with different derivatives of isatin (**2a**–**2zg**) (Table 2). The reaction of 1-naphthol (**1a**) with *N*-benzyl isatins substituted with electron withdrawing and donating groups (**2b**–**2g**) was performed. 5-Halogen substituted *N*-benzyl isatins (**2b**–**2e**) yielded adducts (**3b**–**3e**) in 79–84% yield and 65–75% ee, obviating any predictable trend. The reaction of isatins substituted with electron donating groups (5-Me and 5-OMe) gave corresponding adducts **3f** and **3g** in enantiomeric excess of 63% ee and 61% ee; yield of 78% and 80%, respectively. Similarly, no particular trend was observed in case of reaction of *N*-allyl isatin derivatives (**2h**–**2n**) with 1-naphthol. 5-Methoxy-*N*-allyl isatin provided F–C adduct **3n** with the highest level of enantioselectivity (83% ee). *N*-Propargylisatin **2o** gave product **3o** in 80% yield and 58% ee.

The reaction of 4-chloro-1-naphthol (**1b**) with different derivatives of N-substituted isatin (**2p**–**2ze**) afforded corresponding adducts (**3p**–**3ze**) in 72–84% yield and 48–78% ee. The *N*-H isatins derivatives **2zf** and **2zg** react slowly with 4-chloro-1-naphthol to provide corresponding adducts **3zf** and **3zg** in 78% and 79% yield; 49% ee and 37% ee, respectively.

In conclusion, we have developed the organocatalytic enantioselective Friedel–Crafts-type addition reaction of 1-naphthols with isatin derivatives employing bifunctional chiral thiourea–tertiary amine organocatalysts. A wide variety of biologically relevant 3-aryl-3-hydroxy-2-oxindoles have been synthesized in good yield (up to 84%) and good enantioselectivity (up to 83% ee).

Table 2
Substrate scope[a,b,c]



3a 6 hrs 76% yield 77%ee	**3b** 6 hrs 82% yield 74%ee	**3c** 6 hrs 84% yield 65%ee	**3d** 6 hrs 79% yield 66%ee	**3e** 6 hrs 83% yield 75%ee
3f 6 hrs 78% yield 63 % ee	**3g** 6 hrs 80% yield 61 % ee	**3h** 12 hrs 76% yield 48% ee	**3i** 6 hrs 72% yield 63 % ee	**3j** 6 hrs 83% yield 66% ee
3k 6 hrs 84% yield 78% ee	**3l** 6 hrs 78 % yield 65 % ee	**3m** 6 hrs 77% yield 72% ee	**3n** 6 hrs 78% yield 83% ee	**3o** 6 hrs 80% yield 58% ee
3p 6 hrs 82% yield 50% ee	**3q** 6 hrs 80% yield 53% ee	**3r** 6 hrs 79% yield 43% ee	**3s** 12 hrs 81% yield 56% ee	**3t** 8 hrs 84% yield 71% ee
3u 7 hrs 74% yield 60% ee	**3v** 6 hrs 81% yield 56% ee	**3w** 6 hrs 81% yield 60% ee	**3x** 12 hrs 83% yield 60% ee	**3y** 12 hrs 75% yield 62% ee
3z 6 hrs 84% yield 58% ee	**3za** 6 hrs 79% yield 51% ee	**3zb** 6 hrs 77% yield 55% ee	**3zc** 6 hrs 77%yield 52% ee	**3zd** 6 hrs 72% yield 63% ee
3ze 6 hrs 70% yield 61% ee	**3zf** 60 hrs 78% yield 49% ee	3zg 48 hrs 75% yield 37% ee		

[a] Reaction conditions: 0.1 mmol of 1-naphthols **1**, 0.1 mmol isatins **2**, 4 Å molecular sieves (50 mg), and catalysts **I** (10 mol %) in dry THF.
[b] Yield refers to isolated yield after column chromatography.
[c] Enantiomeric excess (ee) determined by chiral HPLC.

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Supplementary data

Supplementary data (detailed experimental procedure and HPLC chromatogram of all compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2014.02.054.

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