# Asymmetric Aza-Friedel–Crafts Reaction of 2-Naphthol with Tosylimines Catalyzed by a Dinuclear Zinc Complex

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**Abstract:** The first asymmetric aza-Friedel–Crafts reaction of 2-naphthol with tosylimines was developed via a dinuclear zinc catalyst (up to 98% ee). It provided a new method for the asymmetric synthesis of Betti base derivatives.

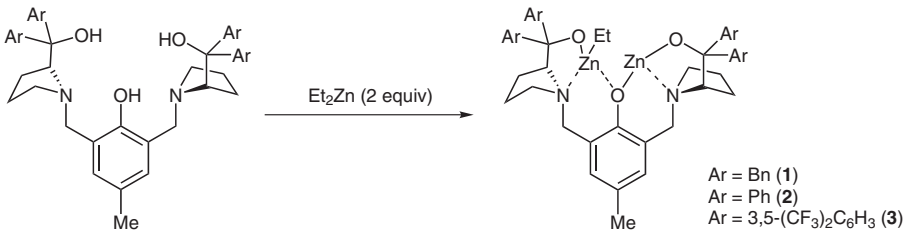
**Key words:** 2-naphthol, asymmetric synthesis, Betti base, Friedel–Crafts reaction, tosylimine

Friedel–Crafts reaction of aromatic substrates to aldehydes, ketones, activated olefines, and imines is a key reaction in synthetic organic chemistry for the formation of carbon–carbon bonds.[1] The stereoselective addition of $sp^2$ C–H bonds to an imine, an aza-Friedel–Crafts reaction, is particularly attractive both because the nucleophiles require no preactivation and because the products are chiral benzylic amines, the substructure exists in many natural products and medicinal chemistry programs.[2] The compounds, especially bearing 1,3-amino-oxygenated functional motifs, are ubiquitous to a variety of potent drugs, including a number of nucleoside antibiotics and HIV protease inhibitors, such as ritonavir and lipinavir.[3] Since these compounds have multiple centers for chelation with metal ions, they are likely to be potent inhibitors of metalloenzymes containing Fe, Cu, Zn, Co, etc. ions as cofactors.[4] In addition, chiral aminophenols have been reported as excellent chelating agents in metal-catalyzed asymmetric induction in a variety of reactions[5] and as precursors in chiral boranate complexes.[6] Chiral Betti base was proved to be an excellent chiral auxiliary for total syntheses of enantiopure alkaloidal natural products.[7]

During the past decades, indole and its derivatives have been demonstrated to be good substrates for the asymmetric Friedel–Crafts reaction.[8] Recently, the substrates have been expanded successfully to electron-rich benzenes[9a–d] and five-membered aromatic heterocycles.[9e–j] In contrast, the applications of the naphthols in asymmetric Friedel–Crafts reaction have rarely been explored.[10] The first example of enantioselective Friedel–Crafts reaction involving 1-naphthols was reported by Erker and van der Zeijden[10a] using a zirconium trichloride Lewis acid containing a 'dibornacyclopentadienyl' ligand. Recently, Jørgensen,[10b,c] Chen[10d] and Wang[10e] presented the organocatalytic asymmetric Friedel–Crafts reaction of 2-naphthol with azodicarboxylates, nitroolefins, and α,β-unsaturated aldehydes, respectively. However, the enantioselective aza-Friedel–Crafts reaction of 2-naphthol with electron-deficient imines has not been reported up till now.

Since racemic Betti base was achieved, numerous modifications of this reaction surfaced and optically pure Betti base analogues were prepared either by resolution[11] or by induction of chirality using optically active amines or aldehydes.[5,12] The development of new methods for their assembly is therefore of considerable synthetic importance. Herein, we wish to report first asymmetric aza-Friedel–Crafts reaction of 2-naphthol with electron-deficient imines in excellent enantioselectivity, which provided a method for asymmetric synthesis of new Betti base derivatives.

The dinuclear zinc complexes **1**–**3** were prepared as previously method[13] by treating the bis-ProPhenol with 2 equivalents of diethylzinc in toluene at room temperature (Scheme 1). Aza-Friedel–Crafts reaction of 2-naphthol with (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide was first examined,[14] which is a useful way to prepare Betti base derivatives. The desired product could not be




**Scheme 1** Preparation of complexes **1**–**3**

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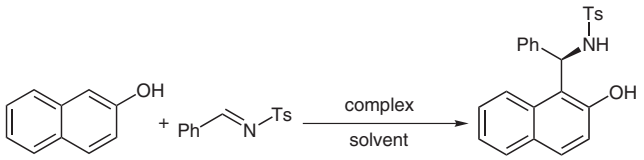
obtained in the absence of complex **2** (Table 1, entry 1). On the other hand, combining 2-naphthol with (*E*)-*N*-benzylidene-4-methylbenzenesulfonamide in the presence of 0.1 equivalents of complex **2** yielded Betti base derivative in 37% yield and 10% ee (entry 2). Increasing the catalyst to 0.3 and 0.5 equivalents could improve the yields and enantioselectivities (entries 3 and 4). The enantioselectivities of the reaction were strongly affected by the reaction conditions. The reaction proceeded at a faster rate and with slightly lower enantiomeric excess at 50 °C (entry 5). In order to obtain a satisfactory result, 1 equivalent of the complex **2** was used and 1-[(*R*)-phenyl(tosylamino)methyl]naphthalen-2-ol (**4a**) was afforded in 90% yield and 96% ee (entry 6). The results showed that dinuclear zinc complexes **1** and **3** gave lower enantioselectivities than complex **2** (entries 7 and 8). Further optimization studies were then carried out using complex **2**. Solvents such as 1,4-dioxane, xylene, $CH_2Cl_2$, and THF were also examined and toluene was found to be the best choice (entries 9–12). Thus, entry 4 in Table 1 was identified as the optimized reaction procedure.

**Table 1** Screening of the Reaction Conditions




| Entry | Complex (equiv) | Temp (°C) | Solvent | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|
| 1 | – | 30 | toluene | n.r. | n.d. |
| 2 | **2** (0.1) | 30 | toluene | 37 | 10 |
| 3 | **2** (0.3) | 30 | toluene | 73 | 55 |
| 4 | **2** (0.5) | 30 | toluene | 82 | 87 |
| 5 | **2** (0.3) | 50 | toluene | 78 | 38 |
| 6 | **2** (1) | 30 | toluene | 90 | 96 (*R*) |
| 7 | **1** (1) | 30 | toluene | 81 | 85 |
| 8 | **3** (1) | 30 | toluene | 95 | 54 |
| 9 | **2** (1) | 30 | dioxane | trace | – |
| 10 | **2** (1) | 30 | xylene | 83 | 86 |
| 11 | **2** (1) | 30 | $CH_2Cl_2$ | 89 | 92 |
| 12 | **2** (1) | 30 | THF | 20 | 24 |

[a] Reaction conditions: 2-naphthol/tosylimine = 1:3 (molar ratio); reaction time: 48 h.
[b] Isolated yield.
[c] Determined by HPLC analysis using Chiralcel OD-H column.

To extend substrate scope, a variety of different imine substrates was further explored under the optimal reaction conditions. As the results summarized in Table 2, the expected products could be obtained in good isolated yields of 82–95% and good to excellent enantioselectivities of 74–98% ee of *R*-configuration for arylimines (entries 1–11). For the less sterically hindered 4-substituted arylimines, the products were obtained in higher enantioselectivities ranging from 90–98% ee (entries 3, 5, 8, 10, and 11). On the other hand, the 2-substituted arylimines gave lower enantioselectivities (entries 2, 4, and 6). Aza-Friedel–Crafts reaction to aliphatic aldimine such as (*E*)-*N*-tosylbutan-1-imine was also examined, and the reaction gave the product in high enantioselectivity of 91% (entry 12). For *N*-Boc imine, the alkylation reaction also proceeded smoothly and *tert*-butyl (2-hydroxynaphthalen-1-yl)(phenyl)methylcarbamate was obtained in 88% yield and 91% ee.

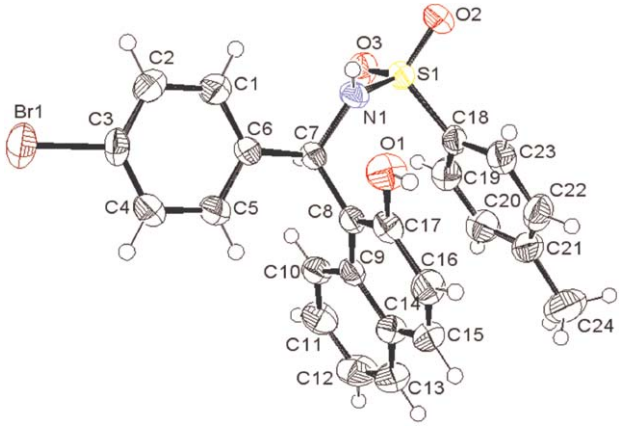
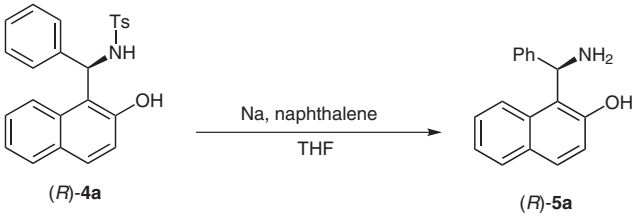



**Figure 1** X-ray crystallography structure of **4k**

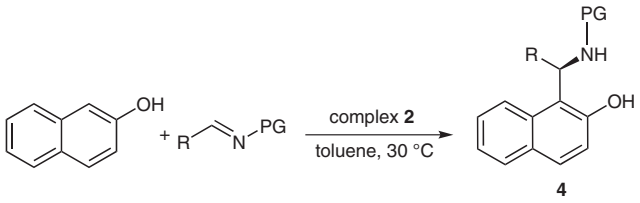
The absolute configuration of the product was confirmed by X-ray crystal structure analysis of Betti base derivative **4k** (Figure 1). On the basis of this structure, compound **4k** possessed an *R*-configuration at the newly formed chiral center.[16] In addition, the absolute configuration of product **4a** was also determined by comparison of the optical rotation of (*S*)-**4a**[17] and (*R*)-**4a**. In order to obtain Betti base **5a**, which was an excellent chiral auxiliary for total syntheses of enantiopure alkaloidal natural products, sodium/naphthalene in dry THF was used to deprotect the Ts group and the (*R*)-Betti base **5a** could be obtained successfully (Scheme 2).[18]




**Scheme 2** Formation of Betti base

A proposed reaction mechanism is shown in Scheme 3. 2-Naphthol is deprotonized by complex **2** accompanied by the formation of one equivalent of ethane. After this, the tosylimine coordinates to this catalyst to form intermedi-

**Table 2** Asymmetric Aza-Friedel–Crafts Reaction of 2-Naphthol with Tosylimines[a]

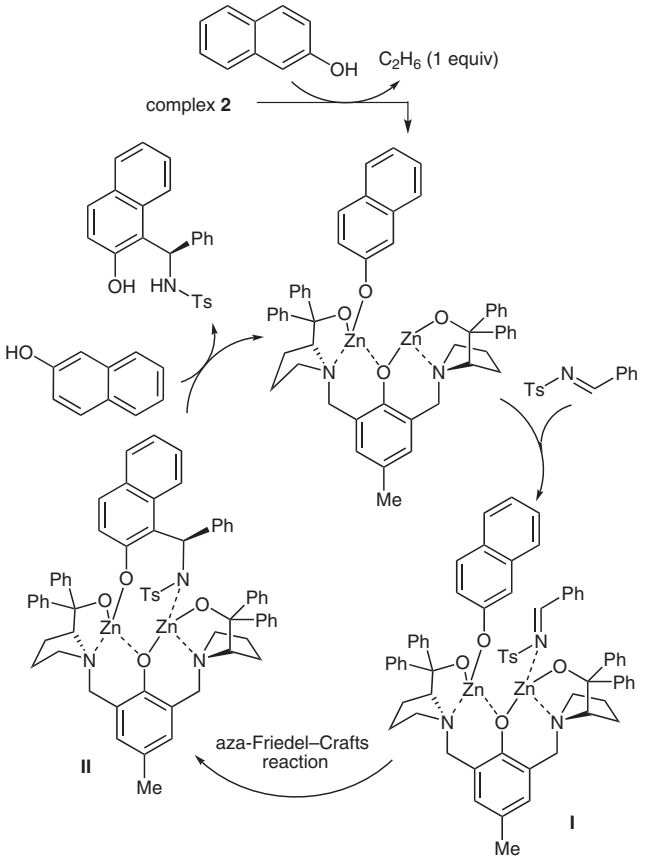



| Entry | R | PG | Product | Yield (%)[b] | ee (%)[c] | Config. |
|---|---|---|---|---|---|---|
| 1 | Ph | Ts | **4a** | 90 | 96 | (–)-(*R*) |
| 2 | 2-$FC_6H_4$ | Ts | **4b** | 92 | 82 | (–) |
| 3 | 4-$FC_6H_4$ | Ts | **4c** | 88 | 93 | (–) |
| 4 | 2-$MeC_6H_4$ | Ts | **4d** | 83 | 83 | (–) |
| 5 | 4-$MeC_6H_4$ | Ts | **4e** | 87 | 90 | (–) |
| 6 | 2-$ClC_6H_4$ | Ts | **4f** | 92 | 80 | (–) |
| 7 | 3-$ClC_6H_4$ | Ts | **4g** | 90 | 74 | (–) |
| 8 | 4-$ClC_6H_4$ | Ts | **4h** | 89 | 98 | (–) |
| 9 | 2-$MeOC_6H_4$ | Ts | **4i** | 91 | 89 | (–) |
| 10 | 4-$MeOC_6H_4$ | Ts | **4j** | 82 | 90 | (–) |
| 11 | 4-$BrC_6H_4$ | Ts | **4k** | 95 | 92 | (–)-(*R*) |
| 12 | Pr | Ts | **4l** | 76 | 91 | (–) |
| 13 | Ph | Boc | **4m** | 88 | 91 | (+) |

[a] Reaction conditions: 2-naphthol/tosylimines/complex **2** = 1:3:1 (molar ratio); reaction time: 48 h.
[b] Isolated yield.
[c] Determined by HPLC analysis using Chiralcel OD-H, OJ-H or AD-H column.[15]

ate **I**, which is followed by aza-Friedel–Crafts alkylation reaction to generate intermediate **II**. The product is then released, and the active catalyst is reformed by a proton exchange between intermediate **II** and an incoming 2-naphthol.

In summary, we have discovered the first highly asymmetric aza-Friedel–Crafts reaction of 2-naphthol with tosylimines for the synthesis of optically active Betti base derivatives. A wide variety of aryl aldimine substrates possessing either electron-withdrawing or electron-donating groups and aliphatic aldimine could be employed successfully. Currently, we are further expanding the application of the Betti base derivatives to catalyze new asymmetric reactions.




**Scheme 3** Proposed reaction mechanism

**Supporting Information** for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

## Acknowledgment

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(13) The preparative procedure of the dinuclear zinc complex, see Supporting Information for full details.

(14) **General Procedure for Aza-Friedel–Crafts Reaction**
To a solution of ligand **2** (r.t., 192 mg, 0.3 mmol) in toluene (4 mL) in a Schlenk tube was added dropwisely a solution of diethylzinc (0.68 mL, 0.6 mmol) under a nitrogen atmosphere. The solution was continued to stir for 1 h to give a solution of complex **2** (0.75 M in toluene). 2-Naphthol (43 mg, 0.3 mmol) and tosylimine (0.9 mmol) were added, and the reaction was stirred for 48 h at 30 °C. After the reaction was completed, the mixture was quenched with sat. $NH_4Cl$ solution (5 mL) and EtOAc (5 mL). The organic layer was separated, and the aqueous phase was extracted with EtOAc (3 × 5 mL). The combined organic layers were dried over $Na_2SO_4$. The solvent was removed under reduced pressure using a rotary evaporator. The residue was purified by column chromatography using $CH_2Cl_2$–PE–EtOAc = 10:10:1 to give the desired product.
***N*-[(2-Hydroxynaphthalen-1-yl)(phenyl)methyl]-4-methylbenzenesulfonamide (4a)**
Yield 90%; light yellow solid; $[\alpha]_D^{20}$ –55 (*c* 1.0, $CHCl_3$); mp 142–144 °C. $^1H$ NMR (400 MHz, $CDCl_3$): δ = 7.72 (d, *J* = 7.2 Hz, 1 H), 7.70 (d, *J* = 4.4 Hz, 1 H), 7.65–7.50 (m, 1 H), 7.40–7.37 (m, 1 H), 7.33–7.30 (m, 5 H), 7.25–7.20 (m, 3 H), 6.87–6.83 (m, 1 H), 6.64 (d, *J* = 8.0 Hz, 3 H), 6.48 (s, 1 H), 6.39 (d, *J* = 8.4 Hz, 1 H), 2.09 (s, 3 H). $^{13}C$ NMR (75 MHz, $CDCl_3$): δ = 151.1, 142.8, 139.9, 135.9, 132.3, 129.6, 128.8, 128.7, 128.3, 127.2, 127.1, 126.7, 126.5, 123.3, 121.8, 118.1, 117.3, 54.4, 21.1. ESI-HRMS: *m*/*z* calcd for $C_{24}H_{21}NO_3S$ + Na: 426.1140; found: 426.1134. HPLC: ee 96% [Chiralcel OD-H, *n*-hexane–*i*-PrOH (95:5), flow rate: 1.0 mL/min]: $t_R$(minor) = 20.36 min; $t_R$(major) = 25.71 min.

(15) The ee of compounds **4a–l** were determined by HPLC using Chiralcel column, see Supporting Information for full details.

(16) The molecular structure of product **4k** was determined by X-ray crystallography. CCDC 751078 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallo-graphic data centre via www.ccdc.cam.ac.uk/data_request/cif or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: +44 (1223)336033.

(17) The preparative procedure of compound (*S*)-**4a**, see Supporting Information for full details.

(18) **Synthesis of Compound (*R*)-5a**
To dry degassed THF (2.5 mL) taken in a round-bottomed flask under nitrogen was added Na metal (69 mg, 3 mmol) following naphthalene (40 mg, 2.9 mmol). The mixture was stirred for 1 h at r.t. To this solution was added a concentrated solution of (*R*)-**4a** (58 mg, 0.14 mmol) in dry THF (3 mL). The reaction was stirred at r.t. overnight. The mixture was quenched by addition of a small amount of $H_2O$ carefully, the solution dried over anhydrous $MgSO_4$ and filtered. The crude mass was purified by column chromatography to give (*R*)-**5a** (21.6 mg, 62%). $^1H$ NMR (300 MHz, $CDCl_3$): δ = 7.74–7.69 (m, 3 H), 7.49–7.35 (m, 2 H), 7.37–7.15 (m, 6 H), 6.16 (s. 1 H). HPLC: ee 94% [Chiralcel OJ, *n*-hexane–*i*-PrOH (70:30), flow rate: 1.0 mL/min]: $t_R$(minor) = 22.35 min; $t_R$(major) = 51.87 min.