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Organocatalytic Enantioselective Friedel–Crafts Reactions of 1-Naphthols with Aldimines

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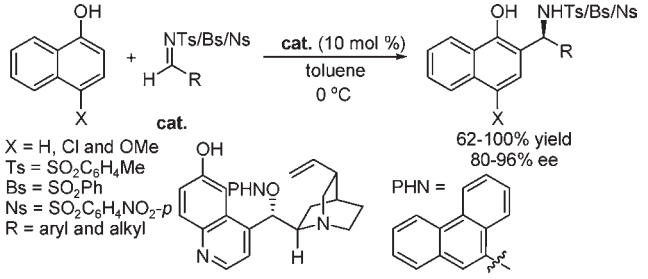
ABSTRACT



An organocatalytic enantioselective Friedel–Crafts reaction of 1-naphthols with aldimines has been developed. The method affords a direct access to chiral aminoarylnaphthols in good yields and with good to high enantioselectivities.

Aminonaphthols are a class of molecules found in a number of natural and synthetic molecules with a wide array of interesting biological activities.[1] Furthermore, chiral aminonaphthol derivatives have been proven to be useful ligands and auxiliaries in asymmetric syntheses.[2] Accordingly, their broad utility has prompted considerable interest to develop asymmetric methods for their preparation. The state-of-the-art in the synthesis of the chiral aminonaphthols largely relies on a diastereoselective reaction using chiral precursors,[2] kinetic resolution,[3] and HPLC enantio-separation of racemics.[4] However, to our knowledge, the catalytic asymmetric version of the synthesis of the chiral scaffold has not been achieved.[5]

Recently impressive enantioselective organocatalytic Friedel–Crafts reactions have been developed.[6] The asymmetric aza-Friedel–Crafts reactions have been demonstrated

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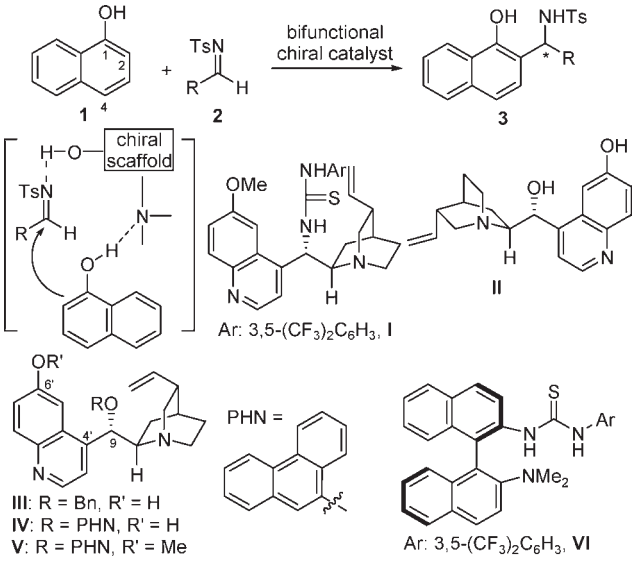
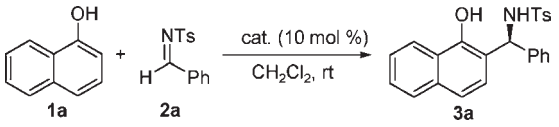
Scheme 1. Bifunctional Catalyst Catalyzed an Asymmetric Aza-Friedel−Crafts Reaction



as valuable tools for the formation of chiral amines.[7] However, significant efforts have been directed toward developing asymmetric organocatalytic Friedel−Crafts reactions using active indoles and pyrroles.[6,7] The asymmetric Friedel−Crafts reaction of naphthols with aldimines represents an attractive approach to the optically active aminoarylnaphthols. While catalytic asymmetric Friedel−Crafts reactions of naphthols with highly active electrophiles have been disclosed,[8,9] the asymmetric Friedel−Crafts reactions with aldimines remain elusive. The reduced electrophilicity of imines in conjunction with regioselectivity renders this transformation difficult. Moreover, naphthols are relatively weak nucleophiles and thus strong Lewis acid activation of electrophiles is generally required.[8] Herein we wish to report a catalytic enantioselective aza-Friedel−Crafts reaction, catalyzed by a bifunctional organocatalyst (Scheme 1).

Table 1. Exploration of Catalytic Asymmetric Friedel−Crafts Reaction of 1-Naphthol (**1a**) with *N*-Ts Phenyl Imine (**2a**)[a]



entry	cat.	t (h)	% yield[b]	% ee[c]
1	**I**	11	92	−42
2	**II**	32	69	−37
3	**III**	48	62	80
4	**IV**	22	76	88
5[d]	**IV**	32	72	83
6[e]	**IV**	18	84	93
7[e,f]	**IV**	72	80	94
8	**V**	24	NR[g]	–
9	**VI**	62	49	−32
10[e,f,h]	**IV**	120	64	92

[a] Unless otherwise specified, the reaction was carried out using **1a** (0.5 mmol) and **2** (0.1 mmol) in the presence of 10 mol % of catalyst in CH_2Cl_2 (0.5 mL) at rt. [b] Isolated yield. [c] Determined by chiral HPLC analysis (chiralpark AS-H). [d] Using **1a** (0.2 mmol) and **2a** (0.1 mmol). [e] Using toluene (0.5 mL) as solvent. [f] The reaction was run at 0 °C. [g] No reaction. [h] 5 mol % **IV** used.

It is noteworthy that to date organocatalytic enantioselective aza-Friedel−Crafts reactions have been mainly carried out by using chiral phosphoric acids due to their strong activation with imines.[7] In contrast, the examples of employment of weak H-bond bifunctional organocatalysts in aza-Friedel−Crafts reactions have not been reported.[10] We envisioned that chiral bifunctional Brønsted acid/base catalysts could serve as an ideal promoter for the asymmetric process (Scheme 1).[11] The capacity of activation of

(5) During our investigation, a study using Trost's bis-ProPhenol dinuclear zinc complex as a chiral inducer (not a catalytic version) in an asymmetric Friedel−Crafts reaction of 2-naphthol with tosylimines has been reported: Niu, L.-F.; Xin, Y.-C.; Wang, R.-L.; Jiang, F.; Xu, P.-F.; Hui, X.-P. *Synlett* **2010**, 765.

(6) For recent reviews on catalytic asymmetric Friedel−Crafts reactions, see: (a) Poulsen, T.; Jørgensen, K. A. *Chem. Rev.* **2008**, *108*, 2903. (b) You, S.-L.; Cai, Q.; Zeng, M. *Chem. Soc. Rev.* **2009**, *38*, 2190. (c) Bandini, M.; Eichholzer, A. *Angew. Chem., Int. Ed.* **2009**, *48*, 9608. (d) Bandini, M.; Umani-Ronchi, A. *Catalytic Asymmetric Friedel-Crafts Alkylations*; Wiley-VCH: Weinheim, 2009. (e) Rueping, M.; Nachtsheim, B. J. Beilstein J. Org. Chem. 2010, 6, No. 6, doi:10.3762/bjoc.6.6. (f) Terrasson, V.; de Figueiredo, R. M.; Campagne, J. M. *Eur. J. Org. Chem.* **2010**, 2635. (g) Zen, M.; You, S.-L. *Synlett* **2010**, 1289.

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(8) Using highly active trifluoromethyl ketones, see: (a) Erker, G.; van der Zeijden, A. A. H. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 512. (b) Johannsen, M. *Chem. Commun.* **1999**, 2233. (c) Ishii, A.; Soloshonok, V. A.; Mikami, K. *J. Org. Chem.* **2000**, *65*, 1597.

(9) Only three examples using highly reactive azodicarboxylates, nitroolefins, and enals with naphthols have been reported; see: (a) Brandes, S.; Bella, M.; Kjærsgaard, A.; Jørgensen, K. A. *Angew. Chem., Int. Ed.* **2006**, *45*, 1147. (b) Liu, T.-Y.; Cui, H.-L.; Chai, Q.; Long, J.; Li, B.-J.; Wu, Y.; Ding, L.-S.; Chen, Y.-C. *Chem. Commun.* **2007**, 2228. (c) Hong, L.; Wang, L.; Sun, W.; Wong, K.; Wang, R. *J. Org. Chem.* **2009**, *74*, 6881.

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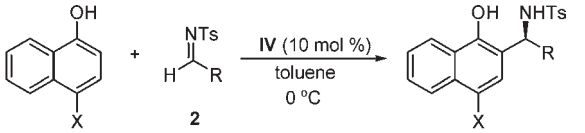
both substrates by a bifunctional catalyst in a cooperative manner would result in high catalytic activity and regio- and enantioselectivity.

To explore the feasibility, a variety of bifunctional catalysts which consist of H-bond donor and amine moieties were screened for a model Friedel–Crafts reaction of 1-naphthol (**1a**) with *N*-Ts phenyl imine (**2**) in CH_2Cl_2 at rt (Scheme 1 and Table 1). The results showed that bifunctional organocatalysts **I**–**VI**[12–14] promoted the reaction smoothly and gave the desired aminonaphthol (**3a**) in moderate to high yields (62–92%, entries 1–4). Notably, in all cases, only one regioisomer was obtained presumably because the proximity of the two functional groups in these catalysts allowed the reaction to proceed at position 2 in **1a**. Although the thiourea **I**[12] can afford two H-bonds (entry 1), it appears that the geometry and stereoconfiguration of the two functional groups is more crucial in controlling activity and enantioselectivity. Catalyst **IV**[13] with one H-bond donor at position 6′ exhibited the most promising results (76% yield and 88% ee, entry 4). Masking the H-bond donor with an OMe group completely demolished the catalyst activity (entry 8), indicating that the H-bond interaction with substrate is essential for both activity and stereoselectivity. In addition, the steric effect imposed at position 9 also plays a role in governing reaction efficiency (entries 3 vs 4). A low ee value and long reaction time were observed for the process promoted by chiral binaphthyl-derived amine thiourea **VI**[14] (entry 9). On the basis of these exploratory studies, we selected catalyst **IV** to further optimize the reaction conditions. Reducing the amount of 1-naphthol decreased the reaction rate, yield, and ee (entry 5). The solvent and temperature effects were also examined. It turned out that the use of 5 equiv of naphthol and 1 equiv of imine with 10 mol % of **IV** in toluene at 0 °C was optimal for the process (80% yield, 94% ee; entry 7). Lowering the catalyst loading (5 mol %) led to a longer reaction time (120 h) and lower yield (64%) (Table 1, entry 10).

To demonstrate the generality of the **IV**-promoted asymmetric imino-Friedel–Crafts reaction, a variety of aldimines and naphthols were explored (Table 2). The results showed that in general the reactions took place efficiently in high yields (63–100%) with good to excellent levels of enantioselectivity (80–95% ee). The processes were applicable to a variety of aldimines **2**, bearing both aryl and alkyl groups (entries 1–16). Aromatic aldimines, regardless of electron-neutral (entry 1), -withdrawing (entries 2–7), and -donating (entries 8–9) substituents on the phenyl ring and the substitution pattern (*ortho*-, *meta*-, or *para*-), participated in this process in high efficiency (62–91% yield and 80–96% ee). Moreover, fused and heterocyclic aromatic aldimines proved to be

Table 2. Catalyst **IV** Promoted Friedel–Crafts Reactions of Naphthols with Imine[a]



entry	X, R, **3**	*t* (h)	% yield[b]	% ee[c]
1	H, Ph, **3a**	72	80	94
2	H, 4-$NO_2C_6H_4$, **3b**	20	88	95
3	H, 3-$NO_2C_6H_4$, **3c**	24	91	94
4	H, 2-$NO_2C_6H_4$, **3d**	24	89	91
5[d]	H, 4-ClC_6H_4, **3e**	28	66	93
6	H, 2-ClC_6H_4, **3f**	22	79	96
7	H, 4-BrC_6H_4, **3g**	120	81	93
8	H, 4-$MeOC_6H_4$, **3h**	96	62	95
9[d]	H, 2-$MeOC_6H_4$, **3i**	40	76	80
10	H, 2-naphthyl, **3j**	18	77	94
11	H, 2-furanyl, **3k**	24	92	93
12	H, $CH_2CH(CH_3)_2$, **3l**	24	63	90
13	H, *n*-C_4H_9, **3m**	48	87	92
14[e]	Cl, Ph, **3n**	24	quant	94
15[e]	OMe, Ph, **3o**	48	97	95
16[e]	H, Ph, **3p**	24	83	94
17[f]	H, Ph, **3q**	13	94	85
18	H, $CH(CH_3)_2$, **3r**	20	55	85

[a] Reaction conditions: unless specified, see footnote *a* in Table 1 and Supporting Information. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] ee value was determined by converting to corresponding TES derivative. [e] *N*-SO_2Ph imine was used. [f] *N*-$SO_2C_6H_4$-NO_2-4 was used.

good acceptors (entries 10 and 11). More significantly, high enantioselectivities for less reactive alkyl aldimines **2** (entries 12, 13, and 18, 85–92% ee) were observed as well. It is noteworthy that no reaction was observed with a highly sterically hindered *t*-BuCHO derived imine presumably due to the significant steric effect. The investigation of 1-naphthols **1** with variation in their electronic features (entries 14–15) revealed that the **IV**-catalyzed processes proceeded smoothly with high ee (91–95%) and high yields (97–100%). Although electron-withdrawing Cl can effectively participate in the reaction (entry 14), no reaction was found for stronger electron-withdrawing substituent NO_2 presumably due to the lower reactivity

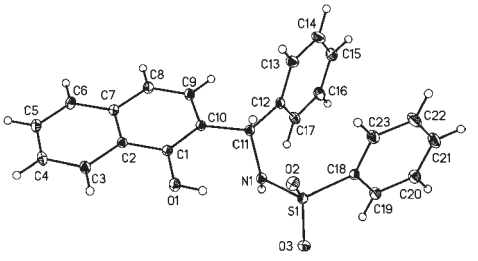


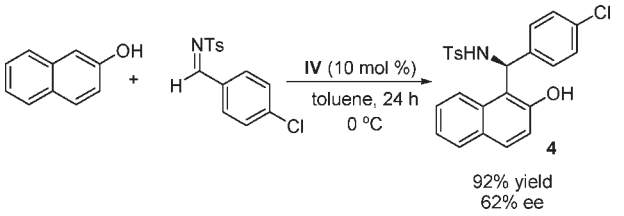
Figure 1. X-ray Structure of Compound **3p** (20% Probability).

(12) Vakulya, B.; Varga, S.; Csampai, A.; Soós, T. *Org. Lett.* **2005**, *7*, 1967.

(13) (a) Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* **2004**, *126*, 9906. (b) Li, H.; Wang, Y.; Tang, L.; Wu, F.; Liu, X.; Guo, C.; Foxman, B. M.; Deng, L. *Angew. Chem., Int. Ed.* **2005**, *44*, 105.

(14) (a) Wang, J.; Li, H.; Yu, X.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4293. (b) Wang, J.; Li, H.; Duan, W.; Zu, L.; Wang, W. *Org. Lett.* **2005**, *7*, 4713.

Scheme 2. Catalyst **IV** Catalyzed Friedel−Crafts Reaction of 2-Naphthol with *N*-Ts Imine



of the hydroxyl group. Finally, changing the protecting group in imines from *N*-Ts to *N*-SO_2Ph (N-Bs) could gain equally good results (83% yield, 94% ee, entry 16). Moreover, the more conveniently removable *N*-Ns imine (*N*-$SO_2C_6H_4$-NO_2-4) was also demonstrated (Table 2, entry 17). The reaction proceeded smoothly to give product **3q** in 94% yield and with 85% ee. It is noted that the 4-nitrophenyl sulfonamide group can be conveniently removed by PhSH in the presence of the K_2CO_3 without racemization (see Supporting Information). The absolute configuration of **3p** was determined by single X-ray crystallographic analysis to be *S* with a heavy atom "sulfur" (Figure 1).[15]

In a preliminary study, we also examined 2-naphthol for the aza-Friedel−Crafts reaction (Scheme 2). Under the same reaction conditions, an exclusive regioselective product **4** was obtained in 92% yield and with a moderate enantioselectivity (62% ee).

In conclusion, driven by the lack of the catalytic asymmetric methods for the preparation of synthetically and medicinally useful chiral aminonaphthols, we have developed new organocatalytic enantioselective imino-Friedel−Crafts reactions. The process is efficiently promoted by a bifunctional organocatalyst **IV** in good yields and with good to high enantioselectivities. A range of aldimines and naphthols can be tolerated in the process. Further investigation of the scope of the reaction and its application in synthesis are underway.

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Supporting Information Available. Experimental procedures and ^{1}H and ^{13}C NMR, elemental analysis, and HRMS data for products **3** and **4** and X-ray crystallographic information of **3p** (CIF file). This material is available free of charge via the Internet at http://pubs.acs.org.

Note Added after ASAP Publication. Reference 7l was added in the version reposted January 24, 2011.

(15) See Supporting Information.