Organocatalytic asymmetric Friedel–Crafts alkylation/cascade reactions of naphthols and nitroolefins†

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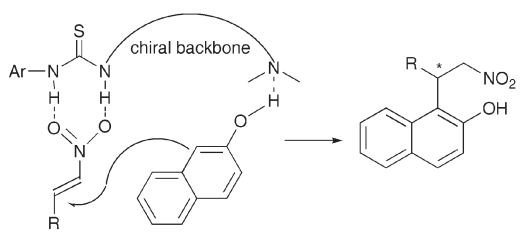
The asymmetric Michael-type Friedel–Crafts reaction of naphthols and nitroolefins promoted by bifunctional thiourea–tertiary amine organocatalysts (up to 95% ee) was investigated; on simply extending the reaction time further cascade reactions could occur to generate enantiopure dimeric tricyclic 1,2-dihydronaphtho[2,1-*b*]furanyl-2-hydroxylamine derivatives.

The Friedel–Crafts (F–C) reaction is a very important process for C–C bond formation in organic chemistry.[1] Various aromatic compounds, including benzenes with electron-donating substituents, furans, pyrroles and indoles, have been successfully applied in a number of F–C reactions with diverse electrophiles, and their enantioselective variants have also been well studied in the presence of chiral metal complexes[2] or small organic molecules.[3] Nevertheless, most reports in this area[4] are still focused on relatively more reactive indole or pyrrole compounds; a few exceptions are the asymmetric F–C reaction of benzene derivatives bearing highly electron-donating groups.[2e] Therefore, there is an urgent requirement to develop novel enantioselective F–C reactions, especially for other undeveloped electron-rich arenes. Naphthols have been demonstrated to be good F–C donors with a range of electrophiles, and thus assorted biologically active compounds or useful chiral ligands for asymmetric catalysis could be facilely prepared.[5,6] However, their applications in catalytic asymmetric F–C reaction have rarely been explored. In 1990, Erker *et al.* reported the enantioselective F–C reaction of 1-naphthol and ethyl pyruvate catalysed by a zirconium trichloride Lewis acid,[5a] and very recently Jørgensen presented the first organocatalytic asymmetric F–C amination of 2-naphthols with azodicarboxylate to form non-biaryl atropisomers.[5b] On the other hand, to the best of our knowledge, the enantioselective Michael-type F–C reaction of naphthols and activated alkenes has not been reported to date.[6]

Recently chiral ureas or thioureas have performed as versatile Brønsted acid catalysts for an array of asymmetric reactions through hydrogen-bonding interaction with various electrophiles.[7] In particular, Ricci *et al.* have presented the first highly enantioselective Michael-type F–C reaction of nitroolefins and indoles catalysed by a thiourea derived from chiral 1-amino-2-indanol.[8] During our continuing studies on organocatalysis based on thiourea compounds,[9] we envisioned that the asymmetric F–C reaction between a nitroolefin and 2-naphthol would be possible, as outlined in Scheme 1, through synergistic activation by a bifunctional thiourea–tertiary amine organocatalyst.[10] In this report, we would like to describe the unprecedented asymmetric Michael-type F–C alkylations of naphthols with nitroolefins in excellent enantioselectivity (up to 95% ee). Furthermore, unexpected and intriguing cascade reactions occurred to give optically pure dimeric 1,2-dihydronaphtho[2,1-*b*]furanyl-2-hydroxylamine derivatives through kinetic resolution under the same catalytic conditions.

A range of bifunctional organocatalysts (Fig. 1) were screened in the F–C reaction of 2-naphthol **2a** and nitrostyrene **3a** in toluene. When thiourea catalyst **1a**[9a] (10 mol%) derived from cinchonine was utilised at ambient temperature, complex mixtures were produced. Fortunately, the desired Michael-type F–C adduct **4aa** was isolated in high yield at lower temperature (−20 °C) after 18 h, along with traces of the byproducts. More gratifyingly, the enantioselectivity was quite promising (Table 1, entry 1, 77% ee). Other similar thiourea–tertiary amine catalysts **1b–1d**[9,10] with different chiral scaffolds gave inferior enantioselectivity under the same conditions (entries 2–4). The bifunctional organocatalysts **1e**[11] and **1f**[8a] also showed good catalytic activity, however, complete racemic product was obtained (entries 5 and 6). This indicated that the combination of thiourea and tertiary amine functionalities was significant to the enantiocontrol. Cinchonine derivative **1g** bearing a less electron-withdrawing group also gave rise to reduced enantioselectivity (entry 7). Consequently we conducted the F–C reaction at −40 °C in the presence of 10 mol% of **1a**. The ee value was dramatically improved, and high yield was



Scheme 1 Proposed Michael-type Friedel–Crafts reaction through concerted activation.

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† Electronic supplementary information (ESI) available: Experimental procedures, structural proofs, NMR and HPLC spectra of the products, CIF files of **4ah** and **5aa**. See DOI: 10.1039/b704925k

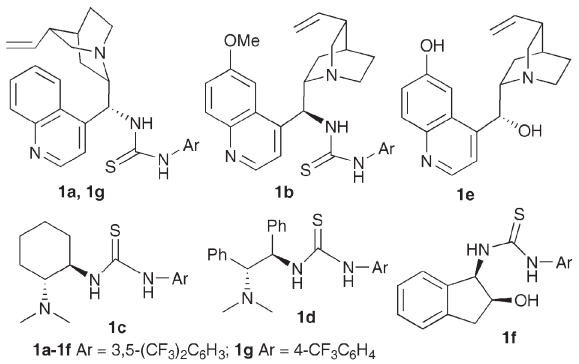
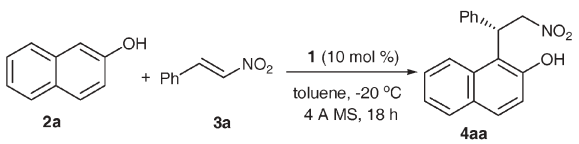


Fig. 1 Structures of various bifunctional organocatalysts.

Table 1 Screening studies of catalytic asymmetric Friedel–Crafts reaction of 2-naphthol **2a** and nitrostyrene **3a**[a]



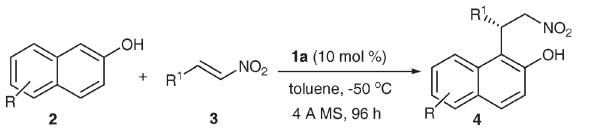
Entry	Catalyst	Yield[b] (%)	ee[c] (%)
1	**1a**	81	77
2	**1b**	77	−63
3	**1c**	73	−59
4	**1d**	61	−37
5	**1e**	78	0
6	**1f**	73	0
7	**1g**	49	53
8[d]	**1a**	85	92
9[e]	**1a**	80	93
10[d,f]	**1a**	72	72

[a] Unless otherwise noted, reactions were performed with 0.1 mmol of **2a**, 0.15 mmol of **3a**, 10 mol% catalyst, in 1 mL toluene at −20 °C for 18 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] At −40 °C for 96 h. [e] At −50 °C for 96 h. [f] In DCM.

attained after 96 h (entry 8). The reaction proceeded smoothly at −50 °C and similar results were obtained (entry 9). Nevertheless, the ee was considerably decreased using DCM as the solvent (entry 10).

Having established the optimal reaction conditions, we then examined a spectrum of naphthols and nitroolefins to explore the generality of this new asymmetric catalysis. The reactions were conducted with 10 mol% of **1a** at −50 °C for 96 h. The results are summarised in Table 2. For the F–C reactions of 2-naphthol **2a**, excellent ee was obtained in the cases of nitrostyrenes **3b** and **3c** with electron-withdrawing substituents (Table 2, entries 2 and 3). Nitroolefins **3d** and **3e** bearing *para*-electron-donating groups gave rise to slightly lower enantioselectivity (entries 4 and 5), while a high ee value was obtained for nitrostyrene **3f** with a *meta*-methyl group (entry 6). Excellent enantioselectivity was observed with heteroaryl substituted nitroolefins **3g** and **3h** (entries 7 and 8). Notably, an outstanding ee was obtained for a simple alkyl-substituted alkene **3i** (entry 9). Subsequently, 2-naphthols **2b** and **2c** bearing electron-donating or -withdrawing groups were investigated, and excellent results were generally achieved (entries 10–13). 1-Naphthol **2d** also exhibited good reactivity with

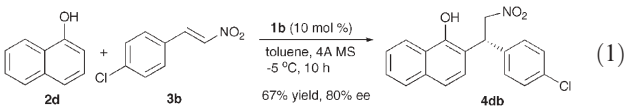
Table 2 Asymmetric Michael-type Friedel–Crafts reaction of 2-naphthols **2** and nitroolefins **3**[a]



Entry	R (**2**)	R^1 (**3**)	**4**	Yield[b] (%)	ee[c] (%)
1	H (**2a**)	Ph (**3a**)	**4aa**	80	93
2	H (**2a**)	*p*-Cl-Ph (**3b**)	**4ab**	82	94
3	H (**2a**)	*p*-F-Ph (**3c**)	**4ac**	81	91
4	H (**2a**)	*p*-Me-Ph (**3d**)	**4ad**	69	85
5	H (**2a**)	*p*-MeO-Ph (**3e**)	**4ae**	74	85
6	H (**2a**)	*m*-Me-Ph (**3f**)	**4af**	72	91
7	H (**2a**)	2-furanyl (**3g**)	**4ag**	77	90
8	H (**2a**)	2-thienyl (**3h**)	**4ah**	79	94[d]
9	H (**2a**)	*n*-Pr (**3i**)	**4ai**	69	94
10	7-MeO (**2b**)	Ph (**3a**)	**4ba**	81	91
11	7-MeO (**2b**)	*p*-Cl-Ph (**3b**)	**4bb**	83	95
12	6-Br (**2c**)	Ph (**3a**)	**4ca**	72	90
13	6-Br (**2c**)	*p*-Cl-Ph (**3b**)	**4cb**	77	90

[a] Reactions performed with 0.1 mmol of **2**, 0.15 mmol of **3**, 10 mol% of **1a** in 1 mL toluene at −50 °C for 96 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. [d] The absolute configuration of **4ah** was determined by X-ray analysis of its *p*-tosylate (see ESI), and other products were assigned accordingly.

nitroolefin **3b**, while better results could be attained catalysed by **1b** derived from quinine at −5 °C (eqn 1).



(1)

Interestingly, during the study of F–C reaction of **2a** and **3a** we were able to isolate an unpredicted product **5aa** (less than 10% at −50 °C after 96 h), whose structure has been firmly determined by X-ray[12] (Fig. 2) and spectroscopic analysis.‡ In addition, this optically pure dimeric 1,2-dihydronaphtho[2,1-*b*]furanyl-2-hydroxylamine derivative **5aa** could become the major product by extending the reaction time to 144 h (Table 3, entry 1). Furthermore, we investigated other combinations of various 2-naphthols and nitroalkenes, and all the reactions generated similar dimeric tricyclic products with full stereocontrol (entries 2–7).

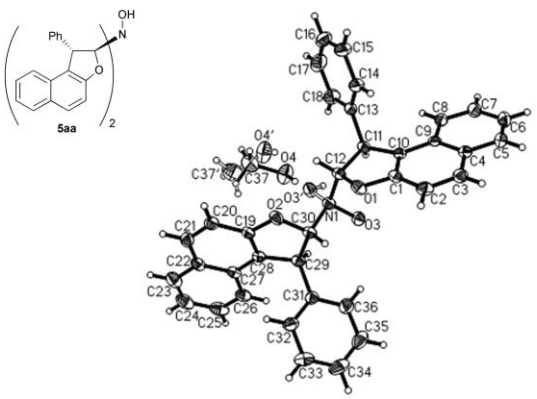
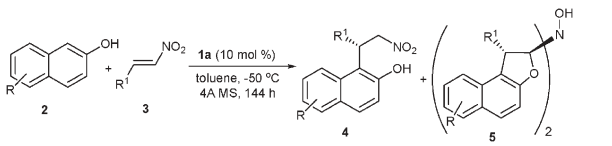


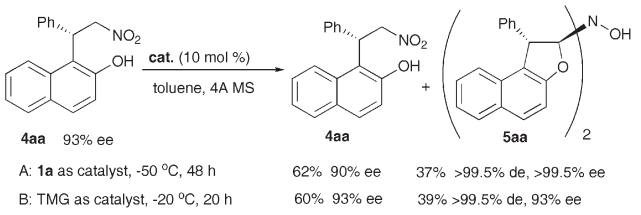
Fig. 2 X-ray structure of racemic **5aa** (a CH_3OH was incorporated in the crystal structure). Thermal ellipsoids are shown at 30% probability.

Table 3 Asymmetric Friedel–Crafts/cascade reactions of 2-naphthols **2** and nitroolefins **3**[a]



Entry	2	3	4 (Yield[b]/ee[c]) (%)	5 (Yield[b]/ee[c,d]) (%)
1	**2a**	**3a**	**4aa** (26/90)	**5aa** (64/> 99.5)
2	**2a**	**3b**	**4ab** (23/90)	**5ab** (63/> 99.5)
3	**2a**	**3c**	**4ac** (25/89)	**5ac** (57/> 99.5)
4	**2a**	**3h**	**4ah** (23/90)	**5ah** (61/> 99.5)
5	**2a**	**3i**	**4ai** (35/92)	**5ai** (52/> 99.5)
6	**2b**	**3b**	**4bb** (21/89)	**5bb** (67/> 99.5)
7	**2c**	**3c**	**4cc** (23/91)	**5cc** (64/> 99.5)

[a] Reactions performed with 0.1 mmol of **2**, 0.15 mmol of **3**, 10 mol% of **1a** in 1 mL toluene at −50 °C for 144 h. [b] Isolated yield. [c] Determined by chiral HPLC analysis. The absolute configuration of **4ah** and the relative configuration of **5aa** were determined by X-ray analysis, and other related compounds were assigned accordingly. [d] > 99.5% de was observed.



Scheme 2 Kinetic resolution in the cascade reactions of Friedel–Crafts product **4aa**.

Apparently the further complicated cascade reactions occur from the F–C adduct **4** promoted by the same thiourea–tertiary amine catalyst, and kinetic resolution of **4** is involved in the cascade sequences. This proposal was unambiguously verified by the catalytic reaction with the isolated adduct **4aa** with 93% ee catalysed by **1a**, and only (*S*)-**4aa** could dimerise to give enantiopure **5aa** (Scheme 2, conditions A). In comparison, the same cyclisation reaction could also proceed in the presence of achiral base 1,1,2,2-tetramethylguanidine (TMG), while the ees of the residual **4aa** and the cyclic product **5aa** remained unchanged (conditions B).[13]

Currently studies on the mechanism[14] and extension of the F–C reaction of naphthols are in progress in this laboratory.

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Notes and references

‡ CCDC 642668 (*p*-tosylate of **4ah**) and 642669 (**5aa**). For crystallographic data in CIF or other electronic format see DOI: 10.1039/b704925k

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12 Crystals of racemic **5aa** suitable for X-ray analysis were obtained from a mixture of methanol and DCM. Some positional disorder was observed in the hydroxylamine moiety of **5aa** and the molecule of methanol in the crystal structures. The occupation of O3 or O3′, O4 or O4′, C37 or C37′ in the crystal structures was found to be equal (50%), see CIF file of **5aa** (CCDC 642669).

13 The dimerisation reaction of **4aa** to give **5aa** could not proceed in the absence of catalyst.

14 A plausible mechanism for the cascade dimerisation reactions has been proposed, see ESI.

