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C_3-Symmetric Chiral Trisimidazoline-Catalyzed Friedel-Crafts (FC)-Type Reaction

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Imidazoline-catalyzed enantioselective Friedel–Crafts (FC)-type reactions were established using C_3-symmetric chiral trisimidazolines. The imidazoline catalysts promoted the FC-type reaction of aldimines with 2-naphthols to produce the corresponding adducts in high yields and with up to 99% ee.

Asymmetric organocatalysis is one of the most attractive approaches to synthesize optically pure compounds without using any precious or toxic metals.[1] In particular, chiral organocatalysts with two or more reaction-promoting functional groups, are of ongoing interest in recent enantioselective synthesis.[2] The functionalities on the catalyst activate the substrates by using a synergistic cooperation,[3] creating the products efficiently. Imidazolines have great potential as reaction-promoting units because of their basicity, nucleophilicity, and the Brønsted acidity of their salts.[4] However, chiral imidazolines as organocatalysts have not been adequately studied until now.[5,6] Herein, we report the first chiral imidazoline-catalyzed Friedel–Crafts (FC)-type reaction of aldimines with 2-naphthols. The C_3-symmetric chiral trisimidazolines **1** (Fig. 1) work as powerful organocatalysts for the FC-type reaction producing the adduct in high yields and with high enantioselectivity.

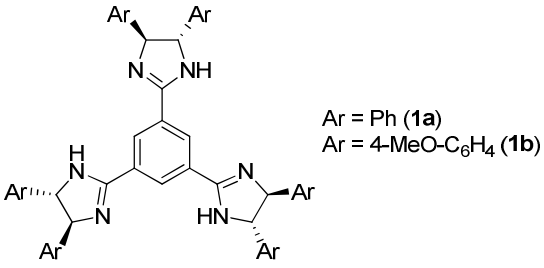


Fig. 1 Chiral trisimidazoline catalysts **1**.

An asymmetric FC-type reaction between phenols and aldimines is an important preparation route of the optically active α-aminomethylphenol unit.[7,8] which is often found in pharmaceutically important compounds[9] and is widely utilized in asymmetric transformations.[10] The first enantioselective FC-type reaction of 2-naphthol and aldimines was presented by Hui[7a] in 2010 using a stoichiometric amount of a chiral zinc complex. In 2011, Wang[7b] and Chimni[7c] independently reported catalytic enantioselective processes using chiral organocatalysts derived from *Cinchona* alkaloids. We[11e] also developed chiral dinuclear vanadium complexes for the enantioselective FC-type reaction *via* a dual activation mechanism.[11]

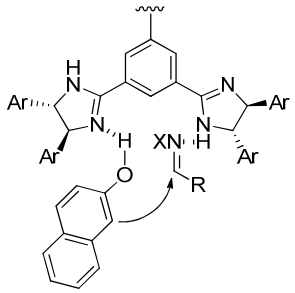
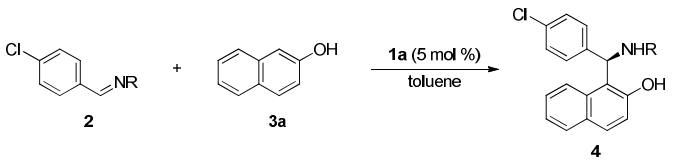


Fig. 2 A plausible transition state for the FC-type reaction of aldimines with 2-naphthols.

Our group previously reported the organocatalytic enantioselective Michael reaction and bromolactonization with trisimidazoline **1a**.[6] We assumed that in the trisimidazoline-catalyzed reaction of aldimines with 2-naphthols, one imidazoline could function as Brønsted base and other imidazoline as a proton donor, leading to a straightforward coupling to produce the adducts in high enantioselectivity (Fig. 2). As the first step in the development of the FC-type process, the reaction of aldimines **2** and 2-naphthol (**3a**) was attempted using a 5 mol % of the chiral trisimidazoline **1a** (Table 1). Among the substituent R imine groups we tested, the aryl sulfonyl groups resulted in products with relatively good yields and moderate enantioselectivities (Table 1, Entries 1-6); the reaction of **2f** (R = 4-Cl-$C_6H_4SO_2$) with **3a** gave the FC adduct **4f** in 40% ee quantitatively (Entry 6).[12] Using more electron deficient aryl sulfonyl groups on the aldimines and lowering the reaction temperature had positive effects on the enantioselectivities (Entries 7-9); the reaction of *N*-4-nosyl imine **2h** (R = 4-NO_2-$C_6H_4SO_2$) produced the FC adduct **4h** in 96% ee (Entry 9).[13,14] The optimal result was obtained when the reaction of **2h** with **3a** was performed in toluene at –5 °C for 36 h (Table 2, Entry 1).

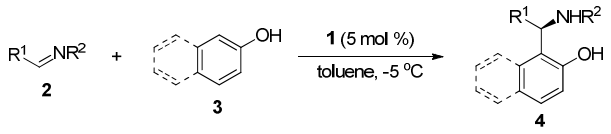
Table 1 Coupling reaction of imines **2** with 2-naphthol (**3a**) mediated by the chiral trisimidazoline catalyst **1a**[a]

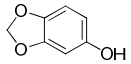


Entry	R	Temp (°C)	Time (h)	Yield (%)[b]	Ee (%)[c]
1	4-Br-C_6H_4 (**2a**)	25	24	82 (**4a**)	*Rac*
2	Boc (**2b**)	25	24	17 (**4b**)	17
3	$PhSO_2$ (**2c**)	25	24	88 (**4c**)	22
4	4-Ts (**2d**)	25	24	70 (**4d**)	27
5	4-MeO-$C_6H_4SO_2$ (**2e**)	25	24	65 (**4e**)	30
6	4-Cl-$C_6H_4SO_2$ (**2f**)	25	12	100 (**4f**)	40
7	**2f**	-5	24	100 (**4f**)	48
8	4-Br-$C_6H_4SO_2$ (**2g**)	-5	24	72 (**4g**)	63
9	4-Ns (**2h**)	-5	24	70 (**4h**)	96

[a]Reaction conditions: **2** (0.1 mmol), **3a** (0.15 mmol), **1a** (5 mol %), toluene (0.4 mL), N_2. [b]Isolated yield. [c]Determined by HPLC (Chiralpak AS-H for **4a**; Chiralpak IB for **4b**; Chiralcel OD-3 for **4c** and **4h**; Chiralpak IC for **4d**; Chiralpak IA for **4e**; Chiralcel OD-H for **4f** and **4g**).

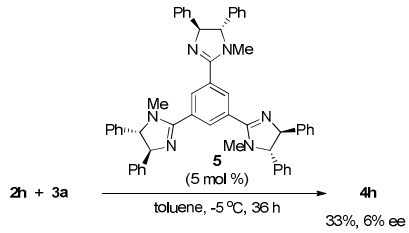
Table 2 Chiral trisimidazoline-catalyzed Friedel-Crafts (FC)-type reaction[a]



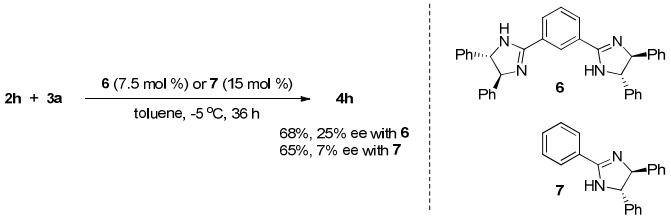
Entry	**1**	R^1	R^2	**3**	Time (h)	Yield (%)[b]	Ee (%)[c]
1	**1a**		**2h**	**3a**	36	89 (**4h**)	96
2	**1a**	3-Cl-C_6H_4	4-Ns (**2i**)	**3a**	48	92 (**4i**)	98
3	**1a**	2-Cl-C_6H_4	4-Ns (**2j**)	**3a**	24	97 (**4j**)	83
4	**1b**		**2j**	**3a**	24	90 (**4j**)	88
5	**1a**	4-Me-C_6H_4	4-Ns (**2k**)	**3a**	36	100 (**4k**)	77
6	**1b**		**2k**	**3a**	36	100 (**4k**)	90
7	**1b**	3-Me-C_6H_4	4-Ns (**2l**)	**3a**	24	95 (**4l**)	99
8	**1b**	3-F-C_6H_4	4-Ns (**2m**)	**3a**	36	98 (**4m**)	85
9	**1b**	4-Br-C_6H_4	4-Ns (**2n**)	**3a**	48	90 (**4n**)	90
10	**1b**	3-NO_2-C_6H_4	4-Ts (**2o**)	**3a**	24	80 (**4o**)	73
11[d]	**1b**	Ph	4-Ns (**2p**)	**3a**	96	100 (**4p**)	73
12	**1b**	2-furyl	4-Ns (**2q**)	**3a**	24	100 (**4q**)	72
13	**1b**		**2h**	6-MeO-2-naphthol (**3b**)	48	90 (**4r**)	77
14[d]	**1b**		**2h**	 **3c**	96	96 (**4s**)	84

[a]Reaction conditions: **2** (0.1 mmol), **3** (0.15 mmol), **1a** (5 mol %), toluene (0.4 mL), -5 °C, N_2. [b]Isolated yield. [c]Determined by HPLC (Chiralcel OD-3 for **4h** and **4s**; Chiralpak AD-H for **4i**, **4k** and **4p-q**; Chiralpak IC-3 for **4l**, **4j**, **4o** and **4r**; Chiralpak IE for **4m**; Chiralcel OD-H for **4n**). [d]At -35 °C.

When *N*-4-nosyl imines **2h-j** containing an electron withdrawing group (R^1 = 4-, 3- or 2-Cl-C_6H_4) were utilized as substrates under the optimal conditions, the organocatalyst **1a** efficiently promoted the reactions with **3a** producing the adducts **4h-j** in high yields and high enantioselectivities (Table 2, Entries 1-3). The catalyst **1a**, mediated the reaction of aldimine **2k**, which possesses an electron rich aromatic ring (R^1 = 4-Me-C_6H_4), to afford the FC product **4k** in 77% ee (Entry 5). However, the use of the newly designed trisimidazoline **1b** which was derived from (1*S*,2*S*)-1,2-bis(4-methoxyphenyl)ethane-1,2-diamine improved the ee value of **4k** (90% ee, Entry 6) while maintaining the high chemical yield. The organocatalyst **1b** also successfully activates the various substrates to afford **4** in high yields and with high enantioselectivity (Entries 4 and 7-11). 2-Furyl *N*-4-nosylimine (**2q**), 6-methoxy-2-naphthol (**3b**), and sesamol (**3c**) were applicable substrates for the reaction (Entries 12-14).[15] The highest enantiomeric excess value was obtained from the reaction of 3-methylphenyl *N*-4-nosyimine (**2l**) with **3a** to give the corresponding adduct **4l** with 99% ee (Entry 7).



Scheme 1. An FC-type reaction catalyzed by *N*-methyl trisimidazoline **5**.



Scheme 2. An FC-type reaction catalyzed by bisimidazoline **6** and monoimidazoline **7**.

The ability of the hydrogen atom attached to the nitrogen in catalyst **1** to play an important role in the promotion of the high enantiocontrol reaction was suggested by the alkylation of *N*-methyl trisimidazoline **5**, where no hydrogen bond-interaction that was depicted in Fig. 2 could be formed and therefore a low yield and a reduced enantioselectivity were observed (Scheme 1). Since a lower enantioselectivity and catalytic activity were observed when using bisimidazoline **6** and monoimidazoline **7** (Scheme 2), the three chiral imidazoline units on catalyst **1** were essential. These units construct three equally-aligned reaction sites, to enable an efficient catalytic activity and highly asymmetric induction ability.

Conclusions

We have discovered the first imidazoline-mediated highly enantioselective FC-type reaction between aldimines **2** and 2-naphthols **3**. Various aryl imine substrates bearing either electron-withdrawing or electron-donating groups could be successfully employed with 5 mol % of the C_3-symmetric chiral trisimidazolines **1**. An investigation into the reaction mechanism and the scope, as well as its application to enantioselective synthesis of biologically active compounds, is currently underway.

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technical staff of the Comprehensive Analysis Center of ISIR, Osaka University (Japan).

Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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12 The results of solvent effect at 25 °C on the reaction giving **4f** were as follows: in DCM: 53% yield, 24% ee; in ClC_6H_5: 33% yield, 23% ee; in tBuOMe: 16% yield, 14% ee, respectively.

13 When the *N*-2- and *N*-3-nosyl imines derived from 4-chlorobenzaldehyde were use as substrates, the ee values of the corresponding FC addcuts drastically dropped to 32% and 36%, respectivly.

14 The *N*-nosyl group on the product **4p** could be removed by benzenethiol with K_2CO_3 without racemization, see ESI.

15 When the ketimine **2r** derived from *N*-benzyl isatine was utilized for the coupling with **3a**, 43% ee of the corresponding product **4t** was obtained in 70% yield, see ESI.