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Organocatalytic Asymmetric Friedel−Crafts Alkylation/Cyclization Cascade Reaction of 1-Naphthols and α,β-Unsaturated Aldehydes: An Enantioselective Synthesis of Chromanes and Dihydrobenzopyranes

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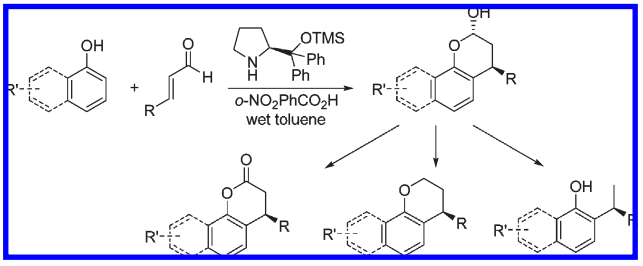

An enantioselective Friedel−Crafts alkylation/cyclization cascade reaction of 1-naphthols and α,β-unsaturated aldehydes promoted by diphenylprolinol ether has been developed. The method affords one-pot access to chiral and synthetically useful chromanes and dihydrobenzopyranes in high yields and enantioselectivities from readily available compounds. In addition, the addition/cyclization products could be afterward transformed to various natural products and biologically active derivatives. On the basis of the experimental results and the observed absolute configurations of the products, a plausible mechanism has been proposed to explain the origin of the activation and the asymmetric induction.

The Friedel−Crafts alkylation is one of the most powerful methods for the formation of a new carbon−carbon bond and has been widely utilized from academic experiments to industrial processes.[1] The asymmetric version of this reaction has attracted considerable interest and witnessed significant progress recently.[2] In spite of considerable effort, most of the successful examples of such a process are focused on relatively more reactive furans, pyrroles and indoles, and a few exceptions are the benzene derivatives bearing highly electron-donating groups.[3] Therefore, there is an urgent requirement to develop novel enantioselective Friedel−Crafts reactions, especially for these undeveloped arenes. Naphthols have been demonstrated to be good Friedel−Crafts donors with a range of electrophiles.[4] However, their applications in catalytic asymmetric Friedel−Crafts reaction have rarely been explored.[5] To the best of our knowledge, the enantioselective Michael-type Friedel−Crafts alkylation of 1-naphthols and α,β-unsaturated aldehydes has not been reported to date.

The chromane and benzopyrane structures are abundant in natural products that possess a broad array of biological activities such as antimicrobial, antiviral, mutagenicity, antiproliferative, sex pheromone, antitumor, and central nervous system activity.[6] Accordingly, a number of synthetic strategies have been developed for the construction of these "privileged" structural motifs.[7] Although many synthetic methods for these

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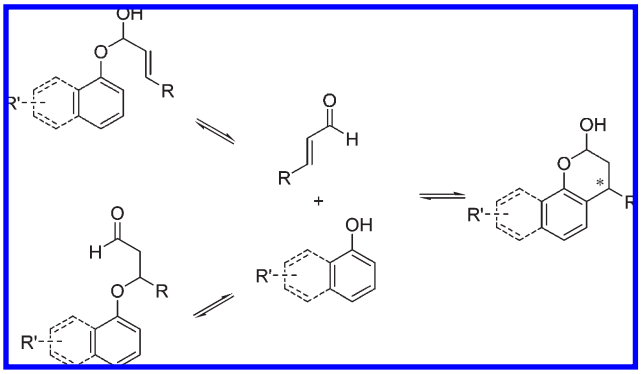
compounds have been reported, most procedures are run under harsh conditions with either high concentrations of acids or large amounts of strong Lewis acids, which can hardly be tolerated by many functional groups. In particular, the enantioselective synthesis of this chiral scaffold has been rarely explored.[8] Given the importance of these valuable chromanes and dihydrobenzopyranes as well as the lack of efficient methods for the preparation of these important active agents, the development of a new catalytic asymmetric synthesis of these compounds appeared to be of great importance. In this context, we reported the organocatalytic asymmetric synthesis of chromanes and dihydrobenzopyranes from readily available 1-naphthols **1** and α,β-unsaturated aldehydes **2** by the Friedel−Crafts alkylation/cyclization cascade reaction.[9]

We envisioned that it might be possible to develope an organocatalytic process[10] for the formation of enantioenriched chromanes and dihydrobenzopyranes by the initial Friedel−Crafts alkylation of 1-naphthol to an α,β-unsaturated aldehyde in the presence of an organocatalyst followed by a subsequent cyclization reaction. However, achieving this process is thought to be difficult because of the competitive addition of oxygen nucleophiles to α,β-unsaturated aldehydes (Scheme 1).[11]

SCHEME 1. Difficulties Encountered When Attempting the Friedel−Crafts Alkylation/Cyclization Cascade Reaction of 1-Naphthol and α,β-Unsaturated Aldehydes



The recent success with the use of diarylprolinol ethers[12] prompted us to try the catalyst **3a** for the asymmetric Friedel−Crafts alkylation/cyclization cascade reaction.[13] We initially investigated the reaction of 1-naphthol **1a** with cinnamaldehyde **2a** in the presence of the catalyst **3a** (10 mol %) and benzoic acid (10 mol %) in THF for 60 h. The product **4a** was formed in low yield probably due to the formation of a rather stable compound **5** (Table 1, entry 1).[14] The same phenomenon was observed in other solvents (Table 1, entries 2−6). To our delight, the addition of water led to a dramatic increase of the yield (Table 1, entries 7 and 8).[15] Apparently, water is helpful for the hydrolysis of intermediate **5** to release the catalyst **3a** and thus enable catalytic turnover. The acid additive also had a great effect on the reaction; almost no reaction occurred when the stronger *p*-toluenesulfonic acid (*p*-TSA) or CF_3CO_2H was used in place of benzoic acid (Table 1, entries 9 and 10). The enantioselectivity could be improved greatly by adding 2-nitrobenzoic acid with a slight decrease of the yield (Table1, entry 12). The screening of different amine catalysts showed that diphenylprolinol ether **3a** was an effective organocatalyst for the reaction in terms of the yield and enantioselectivity (Table1, entries 12−15). To our surprise, catalyst **3b**, a general catalyst for the Michael addition of α,β-unsaturated aldehyde, was not active in the present reaction (Table1, entry 13). After finding the appropriate solvent, acid additive, and catalyst for the reaction, temperature was next screened. Decreasing the reaction temperature to 4 °C resulted in an improved enantioselectivity (95:5 er), but the time required for completion was significantly

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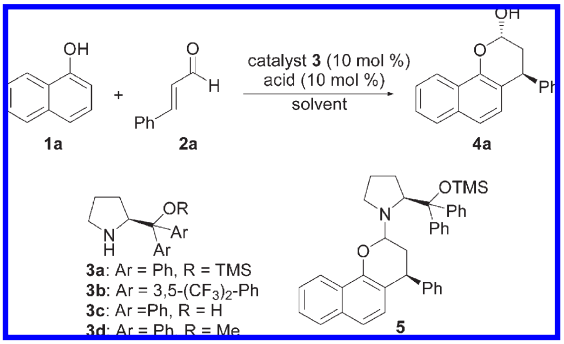
TABLE 1. Reaction Conditions Optimization for the Addition of 1-Naphthol 1a to Cinnamaldehyde 2a[a]



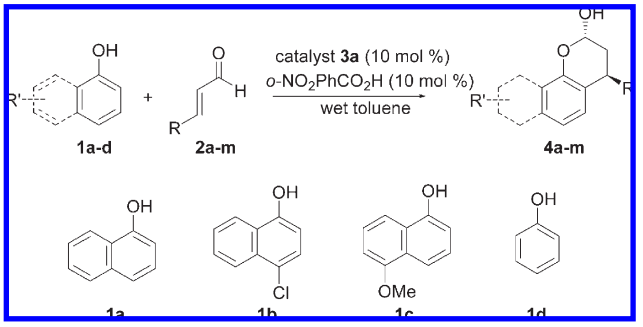
entry	3	acid	solvent	yield (%)[b]	er (%)[c]
1	**3a**	$PhCO_2H$	THF	45	68:31
2	**3a**	$PhCO_2H$	DMSO	28	78:22
3	**3a**	$PhCO_2H$	$CHCl_2$	38	83:17
4	**3a**	$PhCO_2H$	$CHCl_3$	35	86:14
5	**3a**	$PhCO_2H$	ether	44	68:32
6	**3a**	$PhCO_2H$	toluene	51	82:18
7	**3a**	$PhCO_2H$	H_2O	73	85:15
8	**3a**	$PhCO_2H$	toluene/H_2O[e]	85	83:17
9	**3a**	*p*-TSA	toluene/H_2O[e]	< 10	n.d.[d]
10	**3a**	CF_3CO_2H	toluene/H_2O[e]	< 10	n.d.[d]
11	**3a**	AcOH	toluene/H_2O[e]	78	81:19
12	**3a**	*o*-NO_2PhCO_2H	toluene/H_2O[e]	81	92:8
13	**3b**	*o*-NO_2PhCO_2H	toluene/H_2O[e]	< 10	n.d.[d]
14	**3c**	*o*-NO_2PhCO_2H	toluene/H_2O[e]	52	78:22
15	**3d**	*o*-NO_2PhCO_2H	toluene/H_2O[e]	73	85:15
16[f]	**3a**	*o*-NO_2PhCO_2H	toluene/H_2O[e]	43	95:5

[a]Unless otherwise specified, the reaction was carried out with **1a** (0.36 mmol) and **2a** (0.30 mmol) in the presence of an organocatalyst **3** (0.03 mmol), acid (0.03 mmol), and solvent (1.0 mL) for 60 h. [b]Isolated yield of both diastereomers. [c]Determined by chiral HPLC analysis. [d]Not determined. [e]0.15 mmol of H_2O was added. [f]Performed at 4 °C for 120 h.

lengthened (120 h) and the yield was decreased as well (Table1, entry 16). Considering the practical usage, we gave up this condition.

After the optimal conditions had been established, the generality of the cascade Friedel−Crafts alkylation/cyclization processes was explored. As the data show in Table 2, the reactions proceeded in respectively high yields and good levels of enantioselectivities. The process appeared to have a broad scope, but efficiencies and enantioselectivities varied with the electronic nature of the α,β-unsaturated aldehydes **2**. α,β-Unsaturated aldehydes **2** bearing electron-withdrawing groups generally afforded products in higher yields and higher enantioselectivities (Table 2, entries 2−8) than those not possessing electron-withdrawing groups. Relatively lower enantioselectivities were observed for reactions of α,β-unsaturated aromatic aldehydes **2** that bear neutral (Table 2, entry 1) or electron-donating (Table 2, entries 9−11) substituents. The cascade processes also took place with less reactive alkyl or heteroaromatic substituted α,β-unsaturated aldehydes (Table 2, entries 12 and 13), albeit with lower yields and enantioselectivities. It should be noted that the enantioselectivities could be improved to 99:1 er after a single recrystallization (Table 2, entries 1, 6, and 7).

TABLE 2. Organocatalytic Asymmetric Friedel−Crafts Alkylation/Cyclization Cascade Reactions of Representative 1-Naphthols with α,β-Unsaturated Aldehydes[a]



entry	1	R	*t* (h)	yield (%)[b]	dr[c]	er (%)[d]
1	**1a**	Ph (**2a**)	60	81 (**4a**)	7:2	92:8 (> 99:1)[e]
2	**1a**	*o*-Cl-Ph (**2b**)	72	73 (**4b**)	3:1	93:7
3	**1a**	*m*-Cl-Ph (2c)	48	85 (**4c**)	3:1	95:5
4	**1a**	*m*-NO_2-Ph (2d)	24	93 (**4d**)	3:1	93:7
5	**1a**	*p*-F-Ph (**2e**)	48	87 (**4e**)	3:1	92:8
6	**1a**	*p*-Cl-Ph (**2f**)	48	85 (**4f**)	3:1	93:7 (> 99:1)[e]
7	**1a**	*p*-Br-Ph (**2g**)	48	87 (**4g**)	3:1	92:8 (> 99:1)[e]
8	**1a**	*p*-NO_2-Ph (**2h**)	24	91 (**4h**)	3:1	92:8
9	**1a**	*o*-MeO-Ph (**2i**)	84	68 (**4i**)	3:1	90:10
10	**1a**	*m*-MeO-Ph (**2j**)	72	79 (**4j**)	3:1	92:8
11	**1a**	*p*-Me-Ph (**2k**)	72	76 (**4k**)	3:1	91:9
12	**1a**	2-furyl (**2*l***)	84	63 (**4*l***)	7:2	87:13
13	**1a**	Me (**2m**)	60	70 (**4m**)	2:1	86:14
14	**1b**	Ph (**2a**)	72	72 (**4n**)	4:1	88:12
15	**1c**	Ph (**2a**)	60	83 (**4o**)	5:1	92:8
16[f]	**1d**	Ph (**2a**)	168	< 10		
17[g]	**1a**	Ph (**2a**)	84	88 (**4a**)	7:2	92:8

[a]The reaction conditions were the same as those in Table 1, entry 12. [b]Isolated yield of both diastereomers. [c]Diastereomeric ratio determined by ^1H NMR spectroscopy of the crude mixture. [d]Determined by chiral HPLC analysis after $NaBH_4$ reduction of both diastereomers (see the Supporting Information). [e]After a single recrystallization. [f]No reaction. [g]The reaction was performed on a gram scale (20 mmol) for 84 h.

To extend the scope of the reaction further, several other substituted 1-naphthols and phenol were utilized as nucleophiles in the reaction. The reaction proceeded in good yields and enantioselectivities when using 1-naphthol bearing either electron-withdrawing or electron-donating substituents (Table 2, entries 14 and 15). The reaction failed to proceed when the less reactive phenol **1d** was employed (Table 2, entry 16).

Importantly, this reaction could be carried out on a gram scale to demonstrate the synthetic utility of the present system. When the reaction was performed with 20 mmol of **2a** for 84 h, the corresponding adduct **4a** was obtained in high chemical yield without any loss of enantioselectivity (Table 2, entry 17).

The relative configuration of the major product obtained in entry 15 of Table 2 was determined by X-ray diffraction analysis to be 2*S**,4*S** (Figure 1).[16] The absolute stereochemistry at C4 was determined by comparison with a

(16) CCDC-728164 and 728165 contain the supplementary crystallographic data for this paper (**4o** and **6a**, respectively). These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/ data_request/cif.

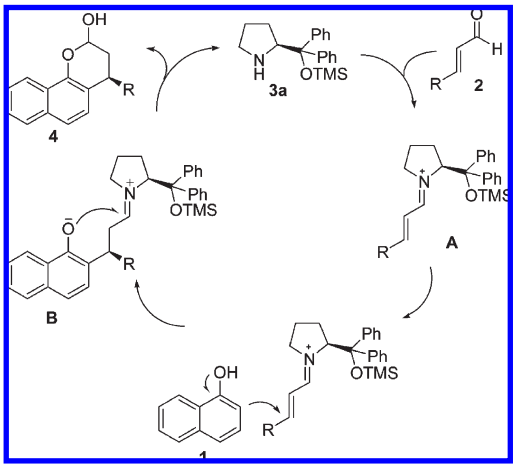


FIGURE 1. Proposed mechanism.

literature known compound **10a**.[17] This was accomplished by dehydroxy-methylation of **6a** with Raney nickel (Scheme 2). By comparing the analytical data and X-ray crystallography, we could establish the stereochemistry of our reaction product **4o** as 2*S*,4*S*.

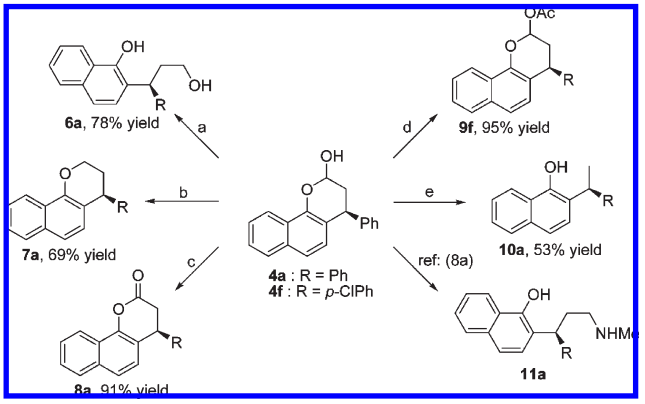
The chromanes **4** are not only components of many natural products, but also valuable substrates for the synthesis of further pharmacologically interesting compounds (Scheme 2). For instance, the reduction of **4a** leads to the formation of **6a** in 78% yield. The chromane **4a** can also be transformed into the corresponding cyclic ether **7a** in two simple steps. Besides, **4a** can be readily oxidized to the benzochromanone **8a** in the presence of PCC. The hydroxy group of **4f** can be acetylated to give **9f**. Furthermore, **4a** can be transformed into fendiline **11a** according to the procedure developed by Hayashi.[8a]

With regard to the mechanism, we assume that the activation of α,β-unsaturated aldehydes **2** by the diphenylprolinol ether **3a** results in the intermediary iminium ion **A**, and then reacts with the 1-naphthol in a 1,4-addition way to give the intermediate **B**. Subsequent hydrolysis and half acetalization provides the desired chromanes **4**, and the catalyst is regenerated (Figure 1).

In summary, we have developed a new organocatalytic asymmetric Friedel−Crafts alkylation/cyclization cascade reaction for the synthesis of chromanes and dihydrobenzopyranes starting from readily available 1-naphthols and α,β-unsaturated aldehydes in good yields and enantioselectivities. Since these compounds could be transformed afterward to various natural products and biologically active derivatives, there is a possibility that this reaction may be developed into a synthetically useful process, although further work is needed to improve both the chemical yield and the enantioselectivity.

(17) (a) Xu, J.; Weiss, R. G. *J. Org. Chem.* **2005**, *70*, 1243–1252. (b) Xu, J.; Weiss, R. G. *Org. Lett.* **2003**, *5*, 3077–3080.

SCHEME 2. Chemical Transformation of 4[a]



[a]**Reaction conditions: (a) $NaBH_4$, MeOH; (b) $NaBH_4$, 20% H_2SO_4; (c) PCC, CH_2Cl_2; (d) Ac_2O, Et_3N, DMAP, CH_2Cl_2; (e) Raney nickel, toluene.**

Experimental Section

General Procedure for the Synthesis of 4. To a solution of catalyst **3a** (0.03 mmol), *o*-NO_2PhCO_2H (0.03 mmol), and α,β-unsaturated aldehyde **2a** (0.30 mmol) in toluene (1.0 mL) and H_2O (30 μL) was added 1-naphthol **1a** (0.36 mmol) at room temperature. The resulting solution was then stirred for 24−84 h. After the complete consumption of the aldehyde (as monitored by TLC), the reaction mixture was poured into water, extracted with EtOAc, dried over Na_2SO_4, evaporated, and then loaded onto silica gel and the products **4a**−**o** were obtained by column chromatography.

(4*S*)-4-Phenyl-3,4-dihydro-2*H*-benzo[*h*]chromen-2-ol (4a). 4a was prepared according to the above method in 81% yield as a mixture of diastereomers (7:2). Major diastereomer: ^{1}H NMR δ 8.27−8.20 (m, 1H), 7.74−7.70 (m, 1H), 7.48−7.41 (m, 2H), 7.33−7.14 (m, 6H), 6.88 (d, J = 8.4 Hz, 1H), 5.78 (s, 1H), 4.42 (dd, J = 9.9, 6.0 Hz, 1H), 3.29 (s, 1H), 2.40−2.32 (m, 1H), 2.25−2.17(m, 1H); ^{13}C NMR δ 146.9, 144.6, 133.5, 128.8, 128.6, 127.5, 127.2, 126.7, 126.0, 125.4, 125.1, 121.6, 120.3, 118.5, 91.6, 37.5, 36.6; IR (film) 3404, 3056, 2934, 1709, 1575, 1497, 1451, 1395, 1261, 1189, 1049, 970, 894, 810, 752, 702; HRMS calcd for $[C_{19}H_{16}O_2 + H]^+$ 277.1223, found 277.1217; $[\alpha]^{rt}_D$ +58 (*c* 1.12, $CHCl_3$); the ee was determined by HPLC analysis, using a Chiralpak OD-H column [hexane/EtOH (90:10)], flow rate 1.0 mL/min, t_{major} = 13.6 min, t_{minor} = 11.8 min (92:8 er).

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Supporting Information Available: Experimental details and characterization data for the products as well as X-ray crystallography of **4o** and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.