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Asymmetric Dearomatization of β-Naphthols through a Bifunctional-Thiourea-Catalyzed Michael Reaction

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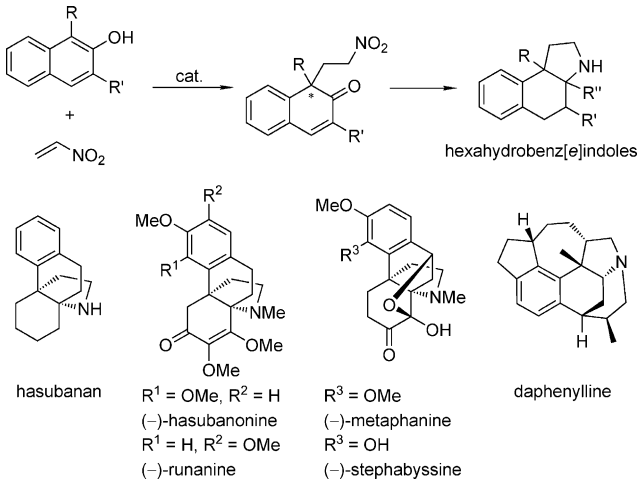
Abstract: *An intermolecular asymmetric dearomatization reaction of β-naphthols with nitroethylene through a chiral-thiourea-catalyzed Michael reaction is described. Enantioenriched functionalized β-naphthalenones with an all-carbon quaternary stereogenic center could thus be easily constructed from simple naphthol derivatives in good yields and excellent enantioselectivity (up to 79% yield, 98% ee).*

The catalytic asymmetric dearomatization (CADA) reaction of phenols and their derivatives has emerged as a powerful method for the construction of enantioenriched multifunctionalized cyclic enones,[1] which are frequently encountered in bioactive natural products and pharmaceuticals. Compared with the well documented enantioselective oxidative dearomatization reactions of phenols,[2] the direct asymmetric dearomatization of phenol derivatives under non-oxidative conditions is limited to alkylation, arylation,[3] and halogenation processes.[4] Recently, we and the Luan group independently reported the asymmetric dearomatization of naphthols by C–N bond-forming addition reactions with different catalytic systems.[5] Notably, Wang and co-workers realized an enantioselective dearomatization of β-naphthols through a ring-opening reaction with *meso*-aziridines.[3f] Despite these elegant contributions, novel catalytic asymmetric dearomatization reactions of phenols and their derivatives are still in great demand. The dearomatization of β-naphthols with nitroethylene[6,7] is particularly attractive as it affords nitroethane-substituted β-naphthalenones, which could be readily converted into the chiral tricyclic hexahydrobenz[*e*]indoles, a class of privileged structural motifs widely distributed in biologically active natural products and therapeutic agents, such as pyrrolidine-fused tetralins, the hasubanan alkaloids, and daphenylline (Scheme 1).[8] In light of the appealing molecular architecture and promising bioactivities of these compounds, significant efforts have been devoted to the development of methods for the construction of this intriguing scaffold.[9] Undoubtedly, novel, efficient, and straightforward processes for the synthesis of this enantioenriched tricyclic skeleton would be highly desirable. Herein, we report an intermolecular asymmetric dearomatization reaction of β-naphthols with nitroethylene in a chiral-thiourea-catalyzed Michael addition reaction.



Scheme 1. Proposed dearomatization of naphthols and selected natural products and biologically active compounds containing a tricyclic hexahydrobenz[*e*]indole core.

The Michael reaction between 1,3-dimethyl-2-naphthol (**2a**) and nitroethylene was chosen as a model reaction to optimize the reaction conditions (Table 1).[10] In the presence of 10 mol% of quinine-derived thiourea catalyst **1a** in toluene at room temperature, the Michael addition reaction proceeded smoothly to afford the desired product **3a** in moderate yield but with excellent enantioselectivity without the observation of the oxa-Michael addition side product (42% yield, 94% *ee*; entry 1). We then screened several bifunctional thioureas and thiocarbamate **1e**, aiming at improving the reaction efficiency and enantioselectivity. Among the catalysts examined, cinchonine-derived thioureas (**1b–1d**) afforded comparable results in terms of yield and enantioselectivity (29–36% yield, 86–90% *ee*; entries 2–4), indicating that the electronic properties of the aryl group of the catalyst did not influence the reaction outcomes significantly. Remarkably, when the Takemoto catalyst **1f**[10a,g] was employed, the desired product **3a** was generated smoothly with improved enantioselectivity (94% *ee*; entry 6). The analogous urea **1g** gave a slightly decreased yield and enantioselectivity (36% yield, 89% *ee*; entry 7). Thiocarbamate **1e**, which bears only one hydrogen-bond donor, proved to be completely ineffective (entry 5), whereas thiourea alone could not promote the dearomatization reaction (see the Supporting Information for details). In the presence of

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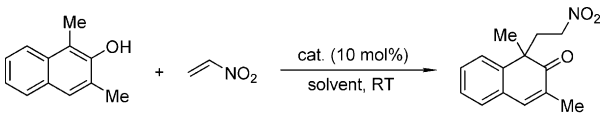
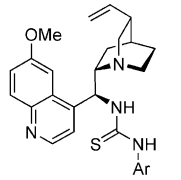
Table 1: Screening of chiral (thio)urea catalysts and optimization of the reaction conditions.[a]

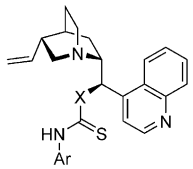


Entry	Catalyst	Solvent	x[b]	t [h]	Yield[c] [%]	*ee*[d] [%]
1	**1a**	toluene	6	27	42	94 (−)
2	**1b**	toluene	6	34	36	90 (+)
3	**1c**	toluene	6	34	29	90 (+)
4	**1d**	toluene	6	22	29	86 (+)
5	**1e**	toluene	4	18	nd	–
6	**1f**	toluene	6	27	40	94 (+)
7	**1g**	toluene	6	29	36	89 (+)
8	quinine	toluene	4	22	20	24 (+)
9	**1a**	CH_2Cl_2	3	22	48	90 (−)
10	**1a**	CCl_4	4	22	38	90 (−)
11	**1e**	CH_2Cl_2	3	22	49	94 (+)
12	**1e**	CCl_4	4	22	36	89 (+)

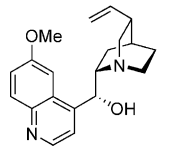
[a] Reaction conditions: catalyst **1** (10 mol%), **2a** (0.2 mmol), and nitroethylene (x equiv) in the indicated solvent (2.0 mL) at room temperature; nitroethylene (2 equiv) was added every 11 h. [b] 2 M solution in toluene. [c] Yield of isolated product. [d] The *ee* values were determined by HPLC analysis on a chiral stationary phase. The sign of the optical rotation is given in parentheses.



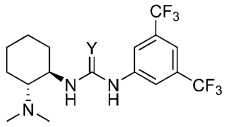
1a: Ar = 3,5-$(CF_3)_2C_6H_3$



1b: X = NH, Ar = 3,5-$(CF_3)_2C_6H_3$
1c: X = NH, Ar = 4-$CF_3C_6H_4$
1d: X = NH, Ar = 4-FC_6H_4
1e: X = O, Ar = 3,5-$(CF_3)_2C_6H_3$



quinine

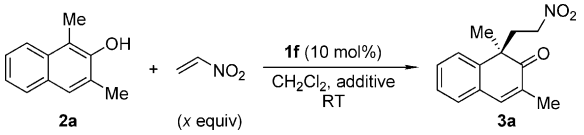


1f: Y = S
1g: Y = O

quinine, the desired product was obtained in low yield and enantioselectivity (20% yield, 24% *ee*; entry 8). These results emphasize the importance of the bifunctionality of the thiourea catalysts. Investigations of the solvent effect disclosed that CH_2Cl_2 is the optimal solvent when the Takemoto catalyst **1f** is employed (entry 11).

Further evaluating several additives revealed that molecular sieves could significantly accelerate the reaction rate and afford improved reaction outcomes in terms of yield and enantioselectivity (62–69% yield, 97% *ee*; Table 2, entries 1–3). Gratifyingly, when one equivalent of nitroethylene was added every hour and the reaction was run with 3 Å molecular sieves as an additive, a dramatic increase in yield without erosion of the enantioselectivity was observed (79% yield, 97% *ee*; entry 6). Further efforts were made to slowly add the nitroethylene by using a syringe pump; the dearomatized product **3a** was thus generated smoothly with no improvement in yield (76% yield, 97% *ee*; entry 7). The absolute configuration of the product was assigned as *R* by vibrational circular dichroism (VCD) spectroscopy (see the Supporting Information for details).[11] When substituted nitroolefins, such as (*E*)-(2-nitrovinyl)benzene and (*E*)-benzyl 3-nitroacrylate, were employed as the Michael acceptors with substrate **2a**, the desired dearomatization reactions did not occur.

Table 2: Additive screening.

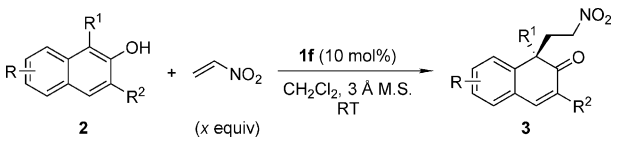


Entry[a]	x	Additive	t [h]	Yield[b] [%]	*ee*[c] [%]
1[d]	2	3 Å M.S.	5.5	69	97
2[d]	2	4 Å M.S.	5.5	62	97
3[d]	2	5 Å M.S.	5.5	65	97
4[e]	2	–	1.5	68	97
5[e,g]	2	3 Å M.S.	1.5	75	98
6[e,g]	2.5	3 Å M.S.	3	79	97
7[f,g]	1.5	3 Å M.S.	2.3	76	95

[a] Reaction conditions: **1f** (10 mol%), **2a** (0.2 mmol), nitroethylene (x equiv), and additive (100 mg) in CH_2Cl_2 (2.0 mL) at room temperature. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase. [d] 1 equiv of **2a** was added every 4 h. [e] 1 equiv of nitroethylene was added hourly. [f] 1.5 equiv of nitroethylene were added by syringe pump over 3 h. [g] 3 Å M.S. (50 mg).

Under the optimized reaction conditions, we next explored the substrate scope of the dearomatization reaction (Table 3). First, various 1,3-disubstituted 2-naphthol derivatives were investigated. When the substituent at the 1-position of 2-naphthol was changed to other groups such as ethyl (**2b**) or allyl (**2c**), the reactions occurred smoothly, delivering the corresponding products in reasonable yields and excellent enantioselectivity (**3b**: 54% yield, 98% ee; **3c**: 68% yield, 94% *ee*). 1-Methyl-2-naphthol derivatives bearing 3-ethyl (**2d**) or 3-benzyl (**2e**) groups were smoothly converted into their corresponding dearomatized products with no erosion of yield or enantioselective control (**3d**: 60% yield, 96% ee; **3e**: 57% yield, 98% *ee*). Furthermore, different groups on the aromatic ring of 1,3-dimethyl-2-naphthol, such as 7-methyl, 7-methoxy, and 7-phenyl substituents, were all well tolerated, affording the dearomatized products in good yields and excellent enantioselectivity (**3f–3h**: 64–67% yield, 93–97% *ee*). We further evaluated a series of 2-naphthols without a substituent at the 3-position, which are challenging substrates in asymmetric dearomatization reactions.[2h,3e] 2-Naphthols bearing different aliphatic groups, such as ethyl, allyl, or benzyl moieties, at the 1-position afforded the corresponding products in good yields and enantioselectivity (**3i–3k**: 59–79% yield, 84-92% *ee*). 1-Methyl-2-naphthols with 6-methoxy, 7-methoxy, or 6-methyl substituents were also suitable substrates, affording the desired products in moderate yields with slightly decreased enantioselectivity (**3l–3n**: 62–68% yield, 83–91% *ee*). To our delight, the 6- or 7-methoxy-substituted 1-allyl-2-naphthol derivatives could be smoothly converted into the corresponding dearomatized products in 78% yield/91% *ee* (**3o**) and 61% yield/92% *ee* (**3p**). 1-Methyl-3-bromo-2-naphthol (**2q**) could not be converted under the current reaction conditions, likely owing to

Table 3: Substrate scope.



Entry[a]	R^1	R^2	R	*x*	*t* [h]	**3**	Yield[b] [%]	*ee*[c] [%]
1	Me	Me	H	2.5	2.5	**3a**	79	97
2	Et	Me	H	4	23	**3b**	54	98
3	allyl	Me	H	3	5	**3c**	68	94
4	Me	Et	H	2	2.5	**3d**	60	96
5	Me	Bn	H	4	4	**3e**	57	98
6	Me	Me	7-Me	3	3	**3f**	67	93
7	Me	Me	7-OMe	3	3	**3g**	64	97
8	Me	Me	7-Ph	4	8	**3h**	67	96
9	Et	H	H	3	4	**3i**	79	92
10	allyl	H	H	4	7	**3j**	64	92
11	Bn	H	H	4	6	**3k**	59	84
12	Me	H	7-Me	3	10	**3l**	68	86
13	Me	H	6-OMe	4	5	**3m**	62	83
14	Me	H	7-OMe	3	4	**3n**	67	91
15	allyl	H	6-OMe	4	6	**3o**	78	91
16	allyl	H	7-OMe	4	5	**3p**	61	92
17	Me	Br	H	4	5	**3q**	–	–

[a] Reaction conditions: **2**, nitroethylene (*x* equiv), **1f** (10 mol%), 3 Å M.S., CH_2Cl_2, room temperature; nitroethylene (1 equiv) was added hourly. [b] Yield of isolated product. [c] Determined by HPLC analysis on a chiral stationary phase.

its low reactivity, which is due to the electron-withdrawing effect of the bromide substituent. Furthermore, substituted phenols, such as 3,5-dimethyl-(1,1′-biphenyl)-4-ol, displayed no reactivity under the optimized reaction conditions.

To demonstrate the synthetic utility of the current method, the dearomatized products were subjected to further transformations (Scheme 2). The reduction of **3n** with iron powder in acetic acid at reflux led to tricyclic product **4** in 86% yield with complete retention of enantiomeric purity. The imine moiety of **4** could be reduced with $NaBH_3CN$, furnishing the pyrrolidine-fused tetralin **5** in 95% yield with high diastereoselectivity. The *N*-tosyl protecting group could be readily introduced into **5** in the presence of TsCl and Et_3N without erosion of the *ee* value (**6**: 92% *ee*). Treatment of product **3j** (92% *ee*) with L-selectride followed by reduction with $LiAlH_4$ and chemoselective protection of the resulting amino alcohol with Boc_2O afforded carbamate **7** in an overall yield of 22% over three steps with good diastereoselectivity (86% *ee*, 4:1 d.r.). Carbamate **7** is a key intermediate in the synthesis of the propellane core structure of the hasubanan alkaloids.[12] This procedure thus also presents a novel approach towards the hasubanan alkaloid family.

A working model of the enantioselectivity-determining transition state was proposed for the current dearomatization reaction (Figure 1).[13] The bifunctionality of Takemoto catalyst **1f** was believed to contribute significantly to the high level of asymmetric induction. The two N–H bonds of the thiourea moiety and the tertiary amine interact with the nitroethylene and the hydroxy group of 2-naphthol, respectively, through hydrogen bonding. Therefore, the two substrates are oriented in a highly ordered conformation, facilitating the *Re* face attack of 2-naphthol to the β-carbon atom of nitroethylene. As a consequence, the dearomatized product is preferentially formed with *R* configuration, which is consistent with the experimental observations.

In conclusion, we have developed an intermolecular asymmetric dearomatization reaction of β-naphthols and nitroethylene through a chiral-thiourea-catalyzed Michael addition reaction. β-Naphthalenones bearing an all-carbon quaternary stereogenic center could be rapidly constructed from naphthol derivatives with excellent enantioselectivity (up to 98% *ee*). The utility of these products was illustrated by the synthesis of aminotetralin and the formal synthesis of the common propellane core structure of the hasubanan alkaloids.

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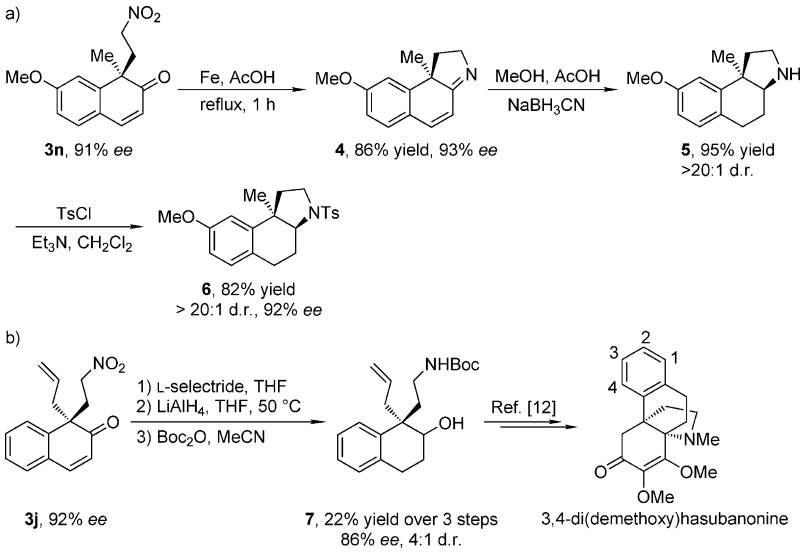

Scheme 2. Further transformations. Boc = *tert*-butoxycarbonyl, Ts = *para*-toluenesulfonyl.

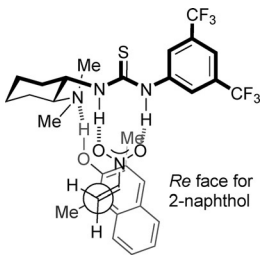

Figure 1. Proposed working model of the enantioselectivity-determining transition state.

Keywords: asymmetric dearomatization · Michael reaction · naphthols · nitroethylene · organocatalysis

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