VIP Asymmetric Hydrogenation

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Catalytic Asymmetric Hydrogenation of Naphthalenes**

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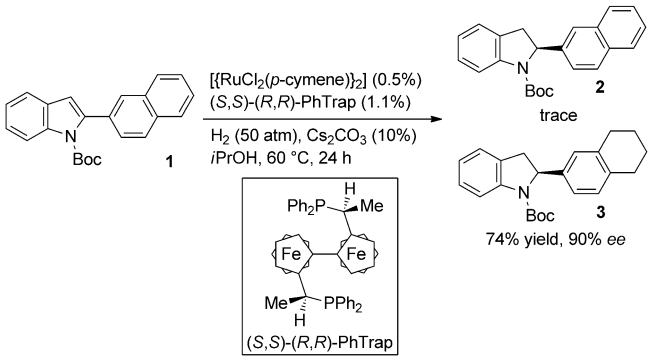
The catalytic asymmetric hydrogenation of heteroarenes has been intensively studied during the last decade.[1] Nowadays, various heteroaromatics, for example, indoles,[2] pyrroles,[3] and quinolines,[4] can be reduced to the corresponding chiral heterocycles with high stereoselectivity through asymmetric catalysis.[5–8] Glorius and co-workers recently found that a chiral N-heterocyclic carbene–ruthenium catalyst allowed the site-selective hydrogenation of the carbocyclic rings of some quinoxalines, producing chiral 5,6,7,8-tetrahydroquinoxalines with up to 88% *ee*.[9–11] However, to the best of our knowledge, the catalytic asymmetric hydrogenation of aromatics containing no heteroatoms remains unexplored.[12,13] Herein, we report the first successful enantioselective hydrogenation of carbocyclic arenes, naphthalenes, through asymmetric catalysis.

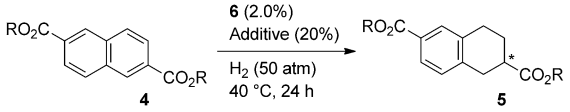
Previously, we had developed the highly enantioselective hydrogenation of *N*-Boc indoles with a ruthenium catalyst generated from [{$RuCl_2$(*p*-cymene)}$_2$] and the chiral bisphosphine ligand, PhTrap.[2d,14] During the course of this study, we attempted the reduction of 2-naphthylindole **1** with the PhTrap–ruthenium catalyst (Scheme 1). To our surprise, none of the expected product **2** was obtained. The hydrogenation was accompanied by the partial reduction of the naphthalene ring, yielding tetrahydronaphthylindoline **3** with 90% *ee*. This observation suggested that the ruthenium complex was capable of reducing carbocyclic aromatic rings. In this context, we began to study the catalytic asymmetric hydrogenation of naphthalenes.



Scheme 1. Asymmetric hydrogenation of 2-naphthylindole. Boc = *tert*-butoxycarbonyl.

In our initial attempt, a solution of dimethyl naphthalene-2,6-dicarboxylate (**4a**) in 1,4-dioxane was stirred at 60°C under hydrogen gas (50 atm) in the presence of [RuCl(*p*-cymene){(*S*,*S*)-(*R*,*R*)-PhTrap}]Cl (**6**)[2d] catalyst. Although formation of the hydrogenation product **5a** was observed, the desired reaction was very sluggish and the enantiomeric excess of **5a** was only 22% *ee* (Table 1, entry 1). Both the stereoselectivity and the reaction rate were affected by the ester substituents of the naphthalene substrate. The reaction of ethyl ester **4b** also proceeded in low yield, but the ethyl substituent brought about a remarkable improvement in the stereoselectivity (entry 2). The use of **4c**, which is a larger and more flexible ester, resulted in a moderate yield of chiral tetralin **5c** (entry 3). The enantiomeric excess of **5c** was improved to 78% *ee* by conducting the hydrogenation at lower temperature (entry 4). The enantioselectivity scarcely

Table 1: Catalytic asymmetric hydrogenation of naphthalene-2,6-dicarboxylate **4**.[a]



Entry	R (**4**)	Additive	Solvent	Conv. [%][b]	*ee* [%][c]
1[d]	Me (**4a**)	Cs_2CO_3	dioxane	17	22
2[d]	Et (**4b**)	Cs_2CO_3	dioxane	18	68
3[d]	*i*Bu (**4c**)	Cs_2CO_3	dioxane	51	69
4	*i*Bu (**4c**)	Cs_2CO_3	dioxane	14	78
5	*i*Bu (**4c**)	–	dioxane	0	–
6	*i*Bu (**4c**)	K_3PO_4	dioxane	24	76
7	*i*Bu (**4c**)	KO*t*Bu	dioxane	28	77
8	*i*Bu (**4c**)	DBU	dioxane	67	82
9	*i*Bu (**4c**)	TMG	dioxane	78	81
10	*i*Bu (**4c**)	DBU	toluene	66	78
11	*i*Bu (**4c**)	DBU	EtOAc	99	81
12	*i*Bu (**4c**)	DBU	EtOH	(79)[e,f]	82
13	*i*Bu (**4c**)	DBU	*i*BuOH	100 (98)[e]	86
14	*i*Bu (**4c**)	DBU	*i*PrOH	100	83

[a] Unless otherwise noted, reactions were conducted on a 0.25 mmol scale in 1.0 mL of solvent at 40°C for 24 h. The ratio of **4**/**6**/additive was 50:1:10. [b] Determined by ^{1}H NMR analysis. Unless otherwise noted, no side product was detected. [c] Determined by HPLC analysis. [d] The reactions were conducted at 60°C. [e] Yields of isolated **5c** are in parentheses. [f] A 14% yield of isolated **5b** was also obtained. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, dioxane = 1,4-dioxane, TMG = 1,1,3,3-tetramethylguanidine.

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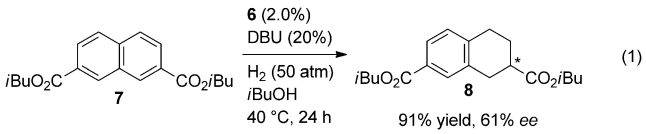
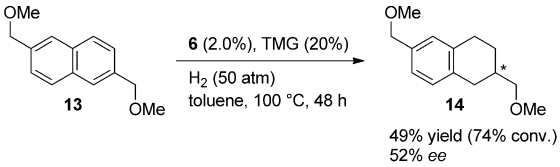
fluctuated with base and solvent, but these factors did influence the catalytic activity of **6**. The absence of a base resulted in no conversion of the naphthalene substrate (entry 5). On the other hand, using either 1,8-diazabicyclo-[5.4.0]undec-7-ene (DBU) or 1,1,3,3-tetramethylguanidine (TMG) as the base led to an increase in the yield of **5c** (entries 8 and 9). The hydrogenation product was quantitatively obtained from reactions carried out in EtOAc or alcoholic solvents (entries 11–14). Isobutyl alcohol is the solvent of choice for the asymmetric hydrogenation of **4c**, as transesterification occurred in other alcohols. Under the optimized conditions, naphthalene **4c** was converted to the desired tetralin **5c** with 86% *ee* (entry 13).[15] The chiral catalyst was also able to hydrogenate 2,7-disubstituted naphthalene **7** to the corresponding chiral tetralin **8** in high yield, but the enantiomeric excess of the product was moderate [Eq. (1)].



(1)

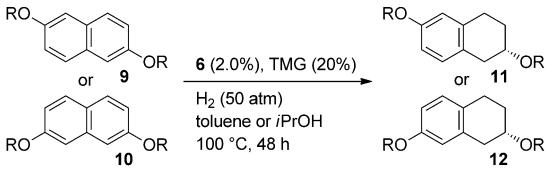
We tested various symmetrical disubstituted naphthalenes in the asymmetric hydrogenation with chiral ruthenium catalyst **6**. 2,6-Dimethoxynaphtalene (**9a**) was quantitatively hydrogenated to the desired tetralin **11a** (Table 2, entry 1). However, the reaction required a higher temperature than for the hydrogenation of **4** or **7**, and proceeded with 69% *ee*. The enantioselectivity was enhanced to 90% *ee* by using an ethoxy- or isopropoxy-substituted substrate (entries 2 and 3). In order to remove the O-alkyl group from the hydrogenation product, THP-protected naphthalenediol **9d** (THP = tetrahydro-2*H*-pyran-2-yl) was employed for the asymmetric transformation. The hydrogenation of **9d** afforded **11d** in high yield (entry 4). The THP groups of **11d** were deprotected by treatment with *p*-toluenesulfonic acid in ethanol to give (*S*)-2,6-dihydroxy-1,2,3,4-tetrahydronaphthalene with 85% *ee*. 2,7-Dialkoxynaphthalenes **10** were also reduced to chiral tetralins **12** through ruthenium catalysis (entries 5–8). As with **9**, ethyl or isopropyl ethers were more favorable for the asymmetric hydrogenation of **10** than methyl ether, giving **12b** or **12c** with 92% *ee*. The chiral ruthenium complex **6** can also catalyze the hydrogenation of bis(alkoxymethyl)naphthalene **13** [Eq. (2)]. However, the reaction proceeded with moderate stereoselectivity and did not reach completion within 48 h. Disappointingly, no reaction was observed when a selection of symmetrical dialkylnaphthalenes were treated with hydrogen in the presence of the PhTrap–ruthenium catalyst. These results suggest that the coordination of an oxygen lone pair in the naphthalene substrate to the ruthenium atom is required for chiral catalysis, as this coordination may induce interaction between the catalyst and the naphthalene ring.



(2)

The low reactivities of dialkylnaphthalenes prompted us to attempt the regio- and enantioselective hydrogenation of unsymmetrical 6-alkyl- or 6-aryl-2-alkoxynaphthalenes **15** (Table 3). Hydrogenation preferentially occurred on the alkoxy-substituted arene ring. In each case, the major product **16** was obtained with 91% *ee*. The substituent at the 6-position had no effect on the stereoselectivity. The reaction of 2-ethoxy-6-ethylnaphthalene (**15a**) gave **16a** and **17a** in a ratio of 79:21 (entry 1). The site-selectivity was also not affected by replacing an ethyl group by a phenyl group at the

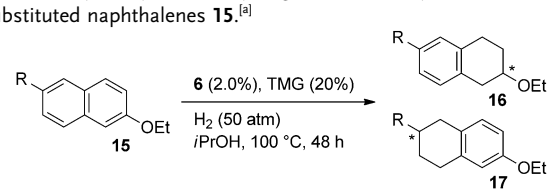
Table 2: Catalytic asymmetric hydrogenation of 2,6- and 2,7-dialkoxynaphthalenes **9** and **10**.[a]



Entry	R (**9** or **10**)	Conv. [%][b]	Product	Yield [%][c]	*ee* [%][d]
1	Me (**9a**)	100	**11a**	99	69
2[e]	Et (**9b**)	100	**11b**	87	90
3	*i*Pr (**9c**)	92	**11c**	91	89
4[e]	THP (**9d**)[f]	96	**11d**	95	85 (*S*)[g]
5	Me (**10a**)	100	**12a**	96	73
6[e]	Et (**10b**)	100	**12b**	97	92
7	*i*Pr (**10c**)	94	**12c**	93	92
8	THP (**10d**)[f]	94	**12d**	90	86 (*S*)[g]

[a] Unless otherwise noted, reactions were conducted on a 0.25 mmol scale in 1.0 mL of 2-propanol at 100°C for 48 h. The ratio of **9** or **10**/**6**/TMG was 50:1:10. [b] Determined by ^{1}H NMR analysis. No side product was detected. [c] Yield of isolated product. [d] Determined by HPLC analysis. [e] The reaction was conducted in toluene. [f] The substrate was a stereoisomeric mixture. [g] The enantiomeric excess was determined after the hydrolytic removal of the THP groups. THP = tetrahydro-2*H*-pyran-2-yl, TMG = 1,1,3,3-tetramethylguanidine.

Table 3: Catalytic asymmetric hydrogenation of unsymmetrical 2,6-disubstituted naphthalenes **15**.[a]

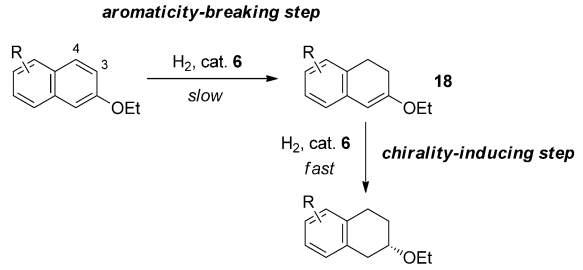


Entry	R (**15**)	Conv. [%][b]	**16**/**17**[b]	Yield [%][c]	*ee* [%][d]
1[e]	Et (**15a**)	100	79:21	65[f]	91
2[g]	Ph (**15b**)	94	79:21	75[h]	91
3	2-MeC_6H_4 (**15c**)	96	96:4	89	91

[a] Unless otherwise noted, reactions were conducted on a 0.25 mmol scale in 1.0 mL of 2-propanol at 100°C for 48 h. The ratio of **15**/**6**/TMG was 50:1:10. [b] Determined by ^{1}H NMR analysis. [c] Yields of isolated products **16**. [d] Enantiomeric excesses of products **16**, as determined by HPLC analysis. [e] The reaction was conducted in toluene with 4% catalyst loading. [f] A 15% yield of isolated **17a** was obtained. [g] The reaction was conducted at 80°C for 24 h. [h] A 21% yield of isolated **17b** with 81% *ee* was obtained.

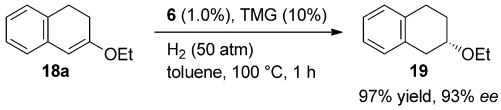
6-position (entry 2). The minor product **17c** was barely formed in the hydrogenation of **15c** (entry 3). The *o*-methyl group in **15c** may sterically hinder the interaction between the catalyst and the aryl-substituted arene ring.

In the present asymmetric hydrogenation, the reduction of the alkoxy-substituted arene ring of naphthalene substrate would be expected to proceed stepwise through sequential 1,2-additions of hydrogen to two C=C bonds as shown in Scheme 2. The less substituted C3–C4 bond is hydrogenated



Scheme 2. Reaction pathway of the asymmetric hydrogenation of naphthalenes.

first to give achiral alkenyl ether **18**. This step partially breaks the aromaticity of the naphthalene, but is not accompanied by chiral induction. Following this, the remaining C=C bond of **18** is rapidly reduced, creating a chiral center in the product. The hydrogenation of **18a** was carried out for the purpose of confirming the above mechanistic consideration [Eq. (3)]. As expected, hydrogenation of the alkenyl ether was complete within 1 h, affording chiral tetralin **19** with 93% *ee*, which is comparable to the enantioselectivities in the hydrogenations of 2-ethoxynaphthalenes **9b**, **10b**, and **15a**–**15c**. In the present asymmetric reaction, the ruthenium complex **6** catalyzes two kinds of hydrogenations: the dearomatizing hydrogenation of naphthalene ring and the catalytic asymmetric hydrogenation of cyclic alkenyl ethers.[16]



(3)

In conclusion, we have found that naphthalenes can be hydrogenated to tetralins by PhTrap–ruthenium catalyst **6**. Furthermore, the chiral ruthenium complex allows the hydrogenation of 2,6- and 2,7-disubstituted naphthalenes to proceed with high enantioselectivity. In particular, 2-alkoxynaphthalenes were converted to the corresponding chiral tetralins with over 90% *ee*. To our knowledge, the present enantioselective reaction is the first success in the catalytic asymmetric hydrogenation of aromatics containing no heteroatoms.[17]

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