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Highly Enantioselective Synthesis of Chiral Cyclic Allylic Amines via Rh-Catalyzed Asymmetric Hydrogenation

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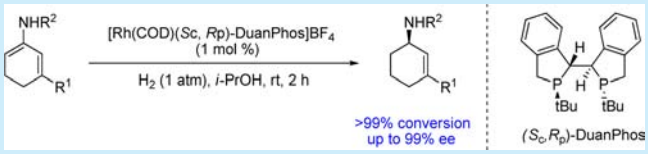
Supporting Information

ABSTRACT: Highly regioselective and enantioselective asymmetric hydrogenation of cyclic dienamides catalyzed by an Rh-DuanPhos complex has been developed, which provides a readily accessible method for the synthesis of chiral cyclic allylic amines in excellent enantioselectivities (up to 99% ee). The products are valuable chiral building blocks and could be easily transformed to multisubstituted cyclohexane derivatives.



Chiral allylic amine moieties exist in many biologically important natural products (Figure 1);[1] therefore,

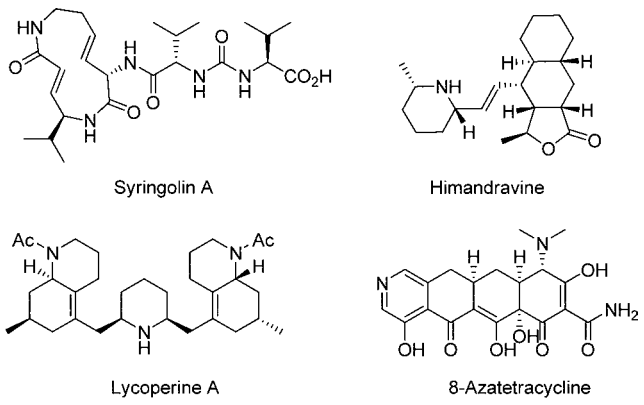


Figure 1. Selected natural products containing chiral allylic amine scaffolds.

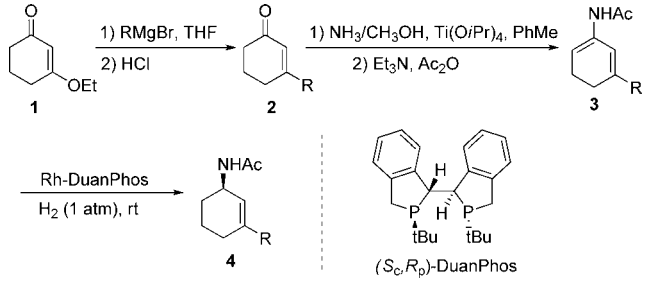
considerable effort has been devoted to the synthesis of chiral allylic amines.[2] The most applied approach to chiral allylic amines is palladium- or iridium-catalyzed enantioselective allylic amination.[3] In addition, several other representative methods, including catalytic asymmetric rearrangement of prochiral allylic imidates,[4] gold-catalyzed intermolecular hydroamination of allenes,[5] and asymmetric addition of potassium alkenyltrifluoroborates to *N*-tosyl imines,[6] have been well documented. However, most of these methods have a limited substrate scope and issues related to activities and selectivities. More importantly, catalytic asymmetric synthesis of chiral cyclic allylic amines is still rare,[3d,7] and enantioselective synthesis of allylic amines remains a significant challenge.

Of particular interest for the synthesis of chiral fine chemicals is asymmetric hydrogenation (AH) for the virtue of high efficiency, atom economy, and cost effectiveness of the methodology. In 1972, Kagan reported their pioneering work on the Rh-catalyzed AH of (*E*)-*N*-(1-phenylprop-1-enyl)-acetamide by using the diphosphine ligand DIOP.[8] Since then, catalytic asymmetric hydrogenation of enamides has been one of the most powerful approaches to synthesize secondary chiral amines and impressive progress has been made.[9]

In the context of our ongoing research in the field of asymmetric hydrogenation, we are always interested in asymmetric hydrogenation of new substrates such as functionalized enamides. Along this line, we recently reported the synthesis of chiral aliphatic amines through asymmetric hydrogenation of dienamides with excellent efficiency and enantioselectivity.[10] We envisioned that the approach might be also suitable for hydrogenation of cyclic dienamides to afford enantiomerically pure cyclic allylic amines. Herein, we report the first regio- and enantioselective hydrogenation of cyclic dienamides in the presence of a chiral rhodium/diphosphine catalyst, giving chiral cyclic allylic amines in high yields and excellent enantioselectivities.

Various cyclic dienamides can be easily prepared from readily accessible corresponding α,β-unsaturated ketones under mild conditions, according to the recently published procedure (Scheme 1).[11] The feasibility of using Rh/diphosphine catalysts generated *in situ* in AHs of cyclic dienamides was first investigated by screening a wide range of diphosphine ligands

Scheme 1. Design and Synthesis of Chiral Allylic Amines



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with *N*-(5-phenylcyclohexa-1,5-dienyl)acetamide (**3a**) as a model substrate (Figure 2). As illustrated in Table 1, except

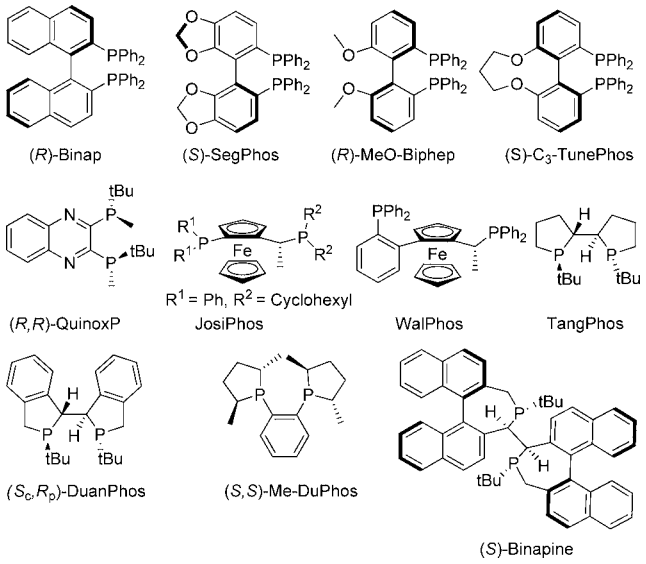
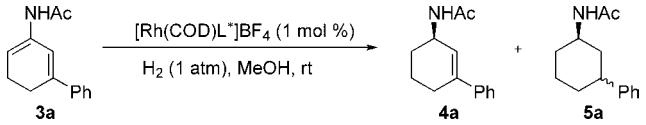


Figure 2. Structures of the phosphine ligands for hydrogenation of cyclic dienamide **3a**.

Table 1. Ligand Screening for Rh-Catalyzed Asymmetric Hydrogenation of Cyclic Dienamide (3a)[a]



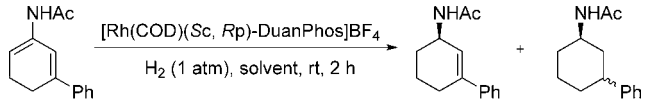
entry	ligand	conversion (%)[b]	4a/5a[b]	ee (%)[c]
1	(*R*)-Binap	>99	95:5	50
2	(*R*)-MeO-Biphep	>99	96:4	69
3	(*S*)-C_3-TunePhos	>99	89:11	50
4	(*S*)-SegPhos	>99	94:6	76
5	(*R,R*)-QuinoxP	51	95:5	46
6	JosiPhos	>99	94:6	2
7	WalPhos	>99	62:38	60
8	(*S,S*)-Me-DuPhos	>99	60:40	95
9	(*S,S*)-Et-DuPhos	>99	51:49	94
10	(*S*)-Binapine	>99	>98:2	35
11	TangPhos	>99	92:8	80
12	(S_c,R_p)-DuanPhos	>99	67:33	97
13[d]	(S_c,R_p)-DuanPhos	>99	>98:2	97

[a]Unless otherwise mentioned, all reactions were carried out with a $[Rh(cod)_2]BF_4$/ligand/substrate ratio of 1:1.1:100, in 1 mL of MeOH at room temperature under hydrogen (1 atm) for 20 h. [b]Determined by ^{1}H NMR spectroscopy. [c]Determined by HPLC analysis using a chiral stationary phase. [d]Completed in 2 h.

for the low activity of (*R,R*)-QuinoxP, all of the tested ligands showed high activity and gave **4a** as a major product, although the enantioselectivity varied to some extent depending on the ligand. Some chiral biaryl bisphosphorus ligands such as Binap, (*R*)-MeO-Biphep, (*S*)-SegPhos, and (*S*)-C_3-TunePhos afforded promising chemoselectivity and moderate enantioselectivity (Table 1, entries 1−4). When chiral ferrocenyl ligands were employed, bad to moderate enantioselectivities were obtained (Table 1, entries 6−7). When (*S,S*)-Me-DuPhos was employed, the enantioselectivity was increased to 95% ee (Table 1, entry 8). Subsequently, electron-donating P-chiral diphosphine ligands developed in our group were screened. It was found that the Rh-DuanPhos catalyst can give excellent enantioselectivity in the hydrogenation of cyclic dienamides (Table 1, entry 12). With a shorter reaction time (2 h), **3a** could be completely transformed to **4a** with excellent enantioselectivity and regioselectivity (Table 1, entry 13).

Encouraged by these promising results, the solvent effect was then investigated. As shown in Table 2, *i*-PrOH was revealed to be the best solvent of choice.

Table 2. Solvent Screening for Rh-Catalyzed Asymmetric Hydrogenation of Cyclic Dienamide (3a)[a]



entry	solvent	conversion (%)[b]	4a/5a[b]	ee (%)[c]
1	MeOH	>99	>98:2	97
2	EtOH	>99	>98:2	97
3	*i*-PrOH	>99	>98:2	98
4	ethyl acetate	>99	>98:2	96
5	CH_2Cl_2	>99	>98:2	96

[a]Unless otherwise mentioned, all reactions were carried out with a catalyst/substrate ratio of 1:100, in 1 mL of solvent at room temperature under hydrogen (1 atm) for 2 h. [b]Determined by ^{1}H NMR spectroscopy. [c]Determined by HPLC analysis using a chiral stationary phase.

Under the optimized reaction conditions, a variety of cyclic dienamides were hydrogenated to afford the corresponding chiral cyclic allylic amines, and the results are presented in Table 3. Gratifyingly, it appears that the position and the electronic property of the substituents on the phenyl rings have little effect on the enantioselectivities (Table 3, entries 1−13). Substrates containing 2-thiophenyl or 2-naphthyl moieties were well applicable (Table 3, entries 14, 15). On the other hand, trienamide **3r** was also investigated to yield the single hydrogenated product with excellent regioselectivity and enantioselectivity (Table 3, entry 18). Remarkably, the AH of cyclic dienamide **3q** containing an alkyne moiety did not lead to the corresponding *N*-(3-(phenylethynyl)cyclohex-2-enyl)-acetamide, but offered (*Z*)-*N*-(3-styrylcyclohex-2-enyl)-acetamide **4q** with comparably high yield, and a slightly lower ee value was observed (Table 3, entry 17).

To further illustrate the potential utility of this method, the hydrogenation of *N*-(5-phenylcyclohexa-1,5-dienyl)acetamide (**3a**) was carried out on gram scale, and the desired product was furnished with 98% yield and 98% ee (Scheme 2a). The remaining C=C bond in product **4** makes it a versatile building block in synthetic chemistry. In the presence of Crabtree's catalyst, the product **4a** could be further hydrogenated in CH_2Cl_2 at room temperature under hydrogen (50 atm), affording enantiomerically pure *N*-(3-phenylcyclohexyl)-acetamide **5a** with a high yield and d.r. value (Scheme 2b). Meanwhile, epoxidation of **4a** was also performed with *m*-CPBA in CH_2Cl_2, giving the desired product **6** in excellent diastereoselectivity and without loss of enantiomeric purity (98% ee, >98:2 d.r.). The ring-opening reaction of epoxide **6** was conducted by using NaN_3 as a nucleophile in hot water, affording product **7** with three contiguous stereogenic centers in excellent enantio- and diastereoselectivities (Scheme 2c).

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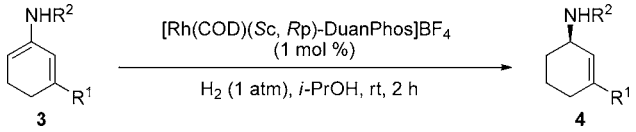
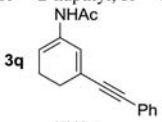
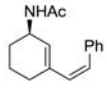
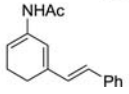
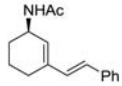
Table 3. Rh-Catalyzed Asymmetric Hydrogenation of Various Cyclic Dienamides (3)[a]

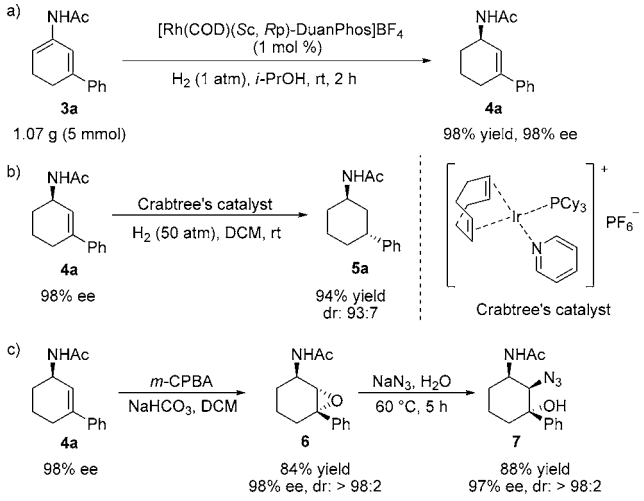


3 4

entry	substrate	product	yield (%)[b]	ee (%)[c]
1	**3a**: R^1 = Ph, R^2 = Ac	**4a**	95	98
2	**3b**: R^1 = 4-F-Ph, R^2 = Ac	**4b**	94	95
3	**3c**: R^1 = 4-Cl-Ph, R^2 = Ac	**4c**	94	97
4	**3d**: R^1 = 4-Br-Ph, R^2 = Ac	**4d**	96	99
5	**3e**: R^1 = 4-CF_3-Ph, R^2 = Ac	**4e**	95	95
6	**3f**: R^1 = 4-Me-Ph, R^2 = Ac	**4f**	93	98
7	**3g**: R^1 = 4-^{t}Bu-Ph, R^2 = Ac	**4g**	96	97
8	**3h**: R^1 = 4-MeO-Ph, R^2 = Ac	**4h**	94	96
9	**3i**: R^1 = 3-F-Ph, R^2 = Ac	**4i**	95	96
10	**3j**: R^1 = 3-Cl-Ph, R^2 = Ac	**4j**	93	95
11	**3k**: R^1 = 3,5-Me-Ph, R^2 = Ac	**4k**	94	98
12	**3l**: R^1 = 3-MeO-Ph, R^2 = Ac	**4l**	96	98
13	**3m**: R^1 = 2-Me-Ph, R^2 = Ac	**4m**	94	92
14	**3n**: R^1 = 2-thienyl, R^2 = Ac	**4n**	95	97
15	**3o**: R^1 = 2-napthyl, R^2 = Ac	**4o**	96	97
16	**3p**: R^1 = 2-napthyl, R^2 = Bz	**4p**	97	98
17	**3q** 	**4q** 	95	91
18	**3r** 	**4r** 	96	97

[a]All reactions were carried out with a catalyst/substrate ratio of 1:100, in *i*-PrOH at room temperature under hydrogen (1 atm) for 2 h, full conversion in all cases. [b]The yield of isolated product based on consumed starting material. [c]Determined by HPLC analysis using a chiral stationary phase.

Scheme 2. Gram-Scale Reaction for AH of 3a, and the Derivatization of 4a



In conclusion, we have developed a highly regioselective and enantioselective asymmetric hydrogenation of cyclic dienamides to afford cyclic allylic amines with excellent enantioselectivities (up to 99% ee) using a commercially available Rh-DuanPhos catalyst. With the mild conditions, broad substrate scope, and readily accessible versatile transformation of cyclic allylic amines, we anticipate it will find broad applications in organic synthesis. Efforts to expand this strategy to other interesting substrates are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures and complete characterizations of the substrates and hydrogenation products (NMR spectra, HPLC chromatograms of racemic and enantioenriched compounds, and HRMS). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) Nakamura, Y.; Burke, A. M.; Kotani, S.; Ziller, J. W.; Rychnovsky, S. D. *Org. Lett.* **2009**, *12*, 72−75. (b) Dai, C.; Stephenson, C. R. J. *Org. Lett.* **2010**, *12*, 3453−3455. (c) Clark, R. B.; He, M.; Fyfe, C.; Lofland, D.; O'Brien, W. J.; Plamondon, L.; Sutcliffe, J. A.; Xiao, X.-Y. *J. Med. Chem.* **2011**, *54*, 1511−1528. (d) Chackalamannil, S.; Davies, R.; McPhail, A. T. *Org. Lett.* **2001**, *3*, 1427−1429.

(2) (a) Cheikh, R. B.; Chaabouni, R.; Laurent, A.; Mison, P.; Nafti, A. *Synthesis* **1983**, *1983*, 685−700. (b) Johannsen, M.; Jørgensen, K. A. *Chem. Rev.* **1998**, *98*, 1689−1708. (c) Ellman, J. A.; Owens, T. D.; Tang, T. P. *Acc. Chem. Res.* **2002**, *35*, 984−995. (d) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921−2944. (e) Burk, M. J.; Allen, J. G.; Kiesman, W. F. *J. Am. Chem. Soc.* **1998**, *120*, 657−663.

(3) (a) Trost, B. M.; Van Vranken, D. L.; Bingel, C. *J. Am. Chem. Soc.* **1992**, *114*, 9327−9343. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev.* **1996**, *96*, 395−422. (c) Ohmura, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 15164−15165. (d) Nemoto, T.; Masuda, T.; Akimoto, Y.; Fukuyama, T.; Hamada, Y. *Org. Lett.* **2005**, *7*, 4447−4450. (e) Helmchen, G.; Dahnz, A.; Dubon, P.; Schelwies, M.; Weihofen, R. *Chem. Commun.* **2007**, 675−691. (f) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258−297. (g) Hartwig, J. F.; Stanley, L. M. *Acc. Chem. Res.* **2010**, *43*, 1461−1475.

(4) (a) Calter, M.; Hollis, T. K.; Overman, L. E.; Ziller, J.; Zipp, G. G. *J. Org. Chem.* **1997**, *62*, 1449−1456. (b) Overman, L. E.; Owen, C. E.; Pavan, M. M.; Richards, C. J. *Org. Lett.* **2003**, *5*, 1809−1812. (c) Anderson, C. E.; Donde, Y.; Douglas, C. J.; Overman, L. E. *J. Org. Chem.* **2005**, *70*, 648−657. (d) Watson, M. P.; Overman, L. E.; Bergman, R. G. *J. Am. Chem. Soc.* **2007**, *129*, 5031−5044.

(5) Butler, K. L.; Tragni, M.; Widenhoefer, R. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 5175−5178.

(6) Gopula, B.; Chiang, C. W.; Lee, W. Z.; Kuo, T. S.; Wu, P. Y.; Henschke, J. P.; Wu, H. L. *Org. Lett.* **2014**, *16*, 632−635.

(7) (a) Trost, B. M.; Oslob, J. D. *J. Am. Chem. Soc.* **1999**, *121*, 3057−3064. (b) Uozumi, Y.; Tanaka, H.; Shibatomi, K. *Org. Lett.* **2003**, *6*, 281−283. (c) Nemoto, T.; Tamura, S.; Sakamoto, T.; Hamada, Y. *Tetrahedron: Asymmetry* **2008**, *19*, 1751−1759.

(8) Kagan, H. B.; Dang Tuan, P. *J. Am. Chem. Soc.* **1972**, *94*, 6429−6433.

(9) (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029−3070. (b) Xie, J. H.; Zhu, S. F.; Zhou, Q. L. *Chem. Rev.* **2011**, *111*, 1713−1760. (c) Zhang, J.; Li, Y.; Wang, Z.; Ding, K. *Angew. Chem., Int. Ed.* **2011**, *50*, 11743−11747. (d) Zhang, X.; Huang, K.; Hou, G.; Cao, B.; Zhang, X. *Angew. Chem., Int. Ed.* **2010**, *49*, 6421−6424. (e) Zhou, M.;

Dong, D.; Zhu, B.; Geng, H.; Wang, Y.; Zhang, X. *Org. Lett.* **2013**, *15*, 5524−5527.
(10) Liu, T.-L.; Wang, C.-J.; Zhang, X. *Angew. Chem., Int. Ed.* **2013**, *52*, 8416−8419.
(11) Reeves, J. T.; Tan, Z.; Han, Z. S.; Li, G.; Zhang, Y.; Xu, Y.; Reeves, D. C.; Gonnella, N. C.; Ma, S.; Lee, H.; Lu, B. Z.; Senanayake, C. H. *Angew. Chem., Int. Ed.* **2012**, *51*, 1400−1404.

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