Asymmetric Hydrogenation

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Synthesis of Chiral Aliphatic Amines through Asymmetric Hydrogenation**

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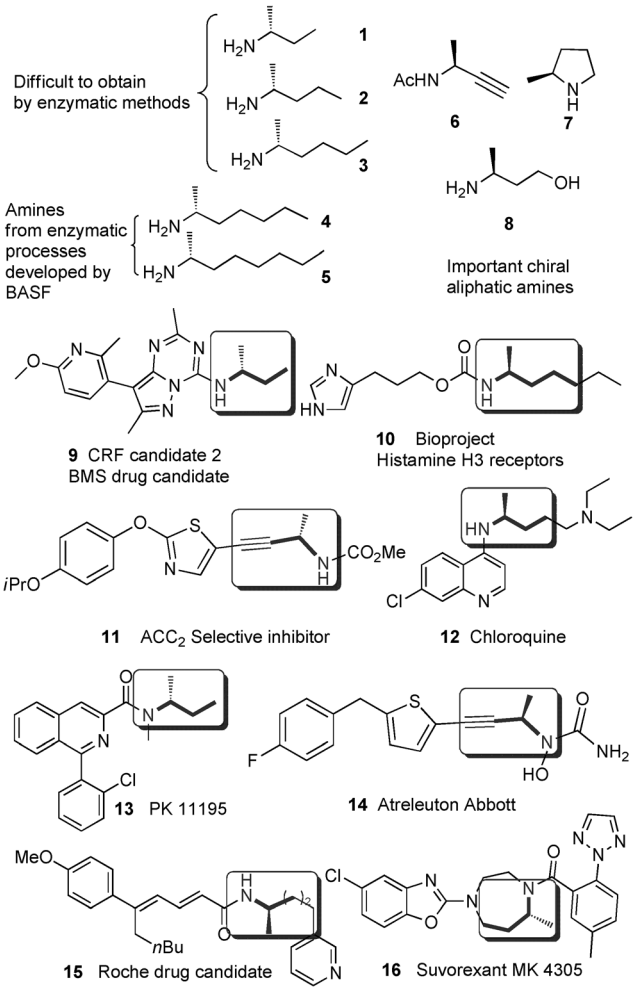
Chiral amines and their derivates are important building blocks for the synthesis of many pharmaceutical and biologically active molecules.[1] Methods for preparing chiral aromatic amines have been developed. The preparation of a series of chiral amines that contain only aliphatic groups proved to be difficult. Among the different types of chiral amines, chiral aliphatic amines are of particular interest, and they were found as key intermediates (**1**–**8**) in drugs and drug candidates such as chloroquine, a corticotropin releasing factor (CRF) drug candidate, suvorexant, dolutegravir, atreleuron, and other biologically active molecules (**9**–**16**; Scheme 1).[2] In comparison with the known methods to generate chiral aromatic amines, less attention was devoted to the synthesis of chiral aliphatic amines. Functionalized aliphatic amines are important chiral amines; aliphatic amines are exemplified by allylic amine, which can be converted to simple aliphatic amines.[3] The preparation of simple chiral aliphatic amines such as 2-aminobutane (**1**) remains a challenging task, and the best enzymatic processes, such as those developed by BASF, for preparing chiral amines could not be used to distinguish a methyl from an ethyl group in the reductive amination of 2-butanone (a major limitation of the enzymatic processes from BASF for the preparation of chiral amines is that the aliphatic amines **1**–**3** are not efficiently prepared). It is highly desired to develop simple and efficient synthetic strategies for the preparation of simple chiral aliphatic amine building blocks, such as those listed in Scheme 1 (**1**–**8**).

Recently, Widenhoefer and co-workers[4] reported a new approach to synthesize chiral allylic amines through a gold-catalyzed intermolecular hydroamination of allenes with moderate yields and enantioselectivities. Common approaches to prepare chiral allylic amines involve the addition of organometallic reagents to ketimines[5] and the intermolecular allylic amination of allylic alcohol derivatives.[6] Among the methods for the preparation of chiral aliphatic allylic amines, the catalytic asymmetric synthesis of allylic amines through transition-metal-catalyzed asymmetric hydrogenation holds a great potential and remains to be developed. Herein, we report the highly enantioselective hydrogenation of (*E*)-*N*-(buta-1,3-dien-2-yl)acetamides catalyzed by a Rh–DuanPhos complex to give directly allylic amines in high yields and enantioselectivities (Scheme 2). Herein we often refer to the products, which are in fact acetamides (acetylated amines), as amines, since the acetyl groups can be easily removed to give the corresponding amines. A number of key chiral aliphatic amine intermediates such as **2**–**6** in Scheme 1 could be prepared by this simple and efficient method.

The Rh-catalyzed asymmetric hydrogenation of *N*-acyl enamines is an elegant efficient method for the enantiose-



Scheme 1. Aliphatic chiral amines and pharmaceutical products. ACC_2 = Acetyl-CoA carboxylase.

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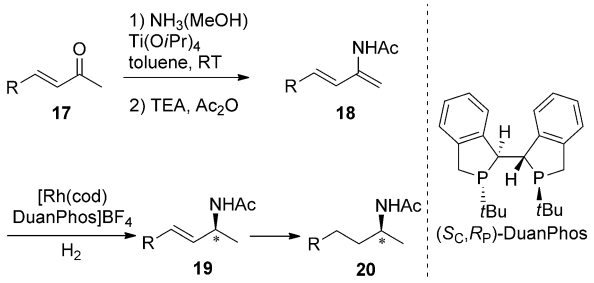


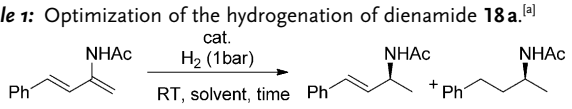
Scheme 2. The design and synthesis of allylic amines. Readily available starting materials (**17**) are used, and the substrates (**18**) are generated in high yields under mild conditions. Enamides (**19**) are obtained with well-defined geometry. cod = cyclooctadiene.

lective synthesis of secondary chiral amines.[7] Since the work reported by Kagan and Dang[8] on the Rh-catalyzed enantioselective hydrogenation of (*E*)-*N*-(1-phenylprop-1-enyl)acetamide by using the diphosphine ligand DIOP, a variety of enamides have been prepared and selectively hydrogenated to obtain secondary chiral amines. However, there are still new enamide substrates that have not been prepared and hydrogenated to produce chiral amines. For example, the chemo- and enantioselective reduction of enamides linked with C=O, C=C double and C≡C triple bonds is a new area. Recently, we reported the selective hydrogenation of ketoenamides and achieved excellent results.[9] Herein, we have developed a new route for the chemo- and enantioselective hydrogenation of dienamides **18** to yield chiral aliphatic allylic amines in high yields and excellent enantioselectivities.

Dienamides can be easily prepared in one step from readily accessible α,β-unsaturated ketones under mild conditions.[10] With (*E*)-*N*-(4-phenylbuta-1,3-dien-2-yl)acetamide (**18a**) as a model substrate, our initial experiment began with [Rh(cod)(S_C,R_P)-DuanPhos]BF_4 in methanol under H_2 (1 bar) for 20 h and offered allylic amine **19a** with 99% *ee*, albeit with a small amount of byproduct **20a** (Table 1, entry 1). With a shorter reaction time (2 h), **18a** could be completely transformed to **19a** with excellent enantioselectivity and chemoselectivity (Table 1, entry 2). Solvent screening revealed that MeOH was the optimal solvent, which led to the best reactivity and selectivity for **19a** (Table 1, entries 2–7). We also tested other chiral ligands, such as TangPhos, ZhangPhos, f-binaphane, and Et-DuPhos; slightly lower reactivities or enantioselectivities were obtained with these chiral ligands. When the catalyst loading was reduced to 0.2 mol%, lower conversion was obtained (Table 1, entries 12 and 13), but changing the catalyst from [Rh(cod)(S_C,R_P)-DuanPhos]BF_4 to [Rh(cod)(S_C,R_P)-DuanPhos]BAr_F, the asymmetric hydrogenation of **18a** was completed with high enantioselectivity (Table 1, entry 14). When using 0.02 mol% of [Rh(cod)(S_C,R_P)-DuanPhos]BAr_F, the reaction still proceeded smoothly with high chemo- and enantioselectivity (Table 1, entry 16). This method is potentially practical for preparing chiral aliphatic amines on a large scale.

Under these optimized reaction conditions (Table 1, entry 2), a variety of (*E*)-*N*-(4-arylbuta-1,3-dien-2-yl)acetamides were hydrogenated, and high chemo- and enantioselectivities were observed (Table 2, entries 1–13). The substituent on the phenyl ring of the substrate had a minor effect on yields and enantioselectivities. All of the tested substrates gave full conversion and excellent enantioselectivities (98–99% *ee*). Dienamides derived from 1- and 2-naphthylaldehyde also worked well in this asymmetric hydrogenation, providing the allylic amines **19l** and **19m** with 99% *ee*, respectively (Table 2, entries 12 and 13). The scope of the Rh-catalyzed asymmetric hydrogenation was not only restricted to 4-aryl dienamides; many 4-alkyl dienamides also performed extremely well, and thus this method provided an alternative for preparing aliphatic chiral amines such as **2–5** (Scheme 1). The catalytic hydrogenation of (*E*)-*N*-(4-alkylbuta-1,3-dien-2-yl)acetamides, such as (*E*)-*N*-(pent-1,3-dien-2-yl)acetamide (**18o**), (*E*)-*N*-(hexa-1,3-dien-2-yl)acetamide (**18p**), and (*E*)-*N*-(4-cyclohexylbuta-1,3-dien-2-yl)acetamide

Table 1: Optimization of the hydrogenation of dienamide **18a**.[a]



Entry	Cat.	Solvent	*t* [h]	S/C	Conv. [%]	**19**/**20**[b]	TON	*ee* [%]
1	**21**	MeOH	20	100	100	91:9	91	98.9
2	**21**	MeOH	2	100	100	>98:2	98	99.6
3	**21**	CH_2Cl_2	2	100	100	85:15	85	92.3
4	**21**	EtOAc	2	100	100	93:7	93	96.5
5	**21**	THF	2	100	100	95:5	95	96.7
6	**21**	$PhCH_3$	2	100	100	98:2	98	98.2
7	**21**	DCE	2	100	100	98:2	98	96.4
8	**22**	MeOH	2	100	100	93:7	93	94.7
9	**23**	MeOH	2	100	100	98:2	98	98.7
10	**24**	MeOH	2	100	100	94:6	94	90.4
11	**25**	MeOH	2	100	100	95:5	94	98.0
12	**21**	MeOH	2	500	65	>98:2	325	98.7
13	**21**	MeOH	20	500	80	95:5	400	98.6
14	**26**	MeOH	20	500	100	>98:2	500	99.6
15	**26**	MeOH	20	1000	100	>98:2	1000	99.6
16	**26**	MeOH	20	5000	100	>98:2	5000	99.5

[a] Reaction conditions: **18** (0.1 mmol), catalyst (0.001 mmol–0.02 μmol), MeOH (1 mL) under 1 bar H_2. S/C = substrate/catalyst ratio, DCE = 1,2-dichloroethane. [b] Determined by NMR spectroscopy. [c] Enantioselectivity was determined by HPLC using a chiral stationary phase.
21: [Rh(cod)(S_C, R_P)-DuanPhos]BF_4; **22**: [Rh(cod)(TangPhos)]BF_4; **23**: [Rh(cod)(ZhangPhos)]BF_4; **24**: [Rh(cod)(f-Binaphane)]BF_4; **25**: [Rh(cod)(Et-DuPhos)]BF_4; **26**: [Rh(cod)(S_C, R_P)-DuanPhos]BAr_F. BAr_F = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

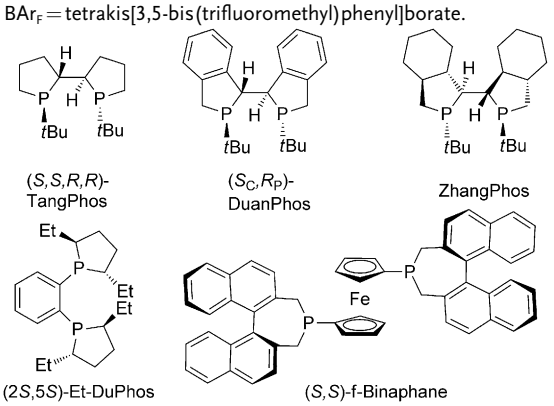
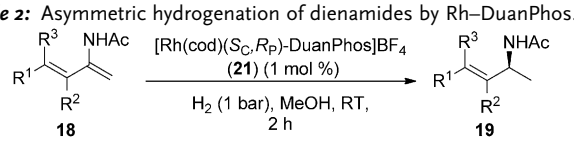
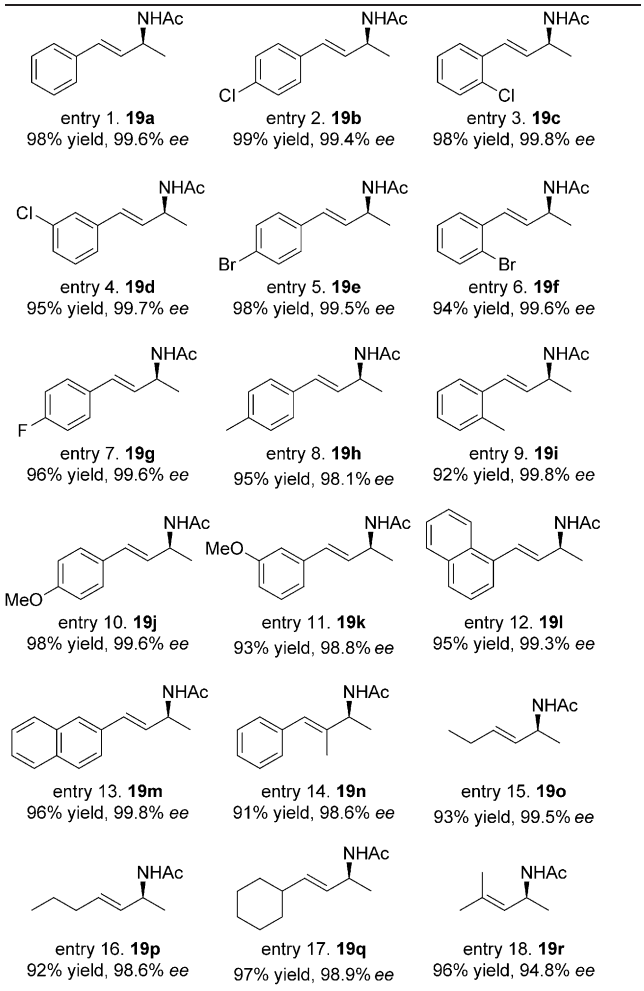


Table 2: Asymmetric hydrogenation of dienamides by Rh–DuanPhos.[a]

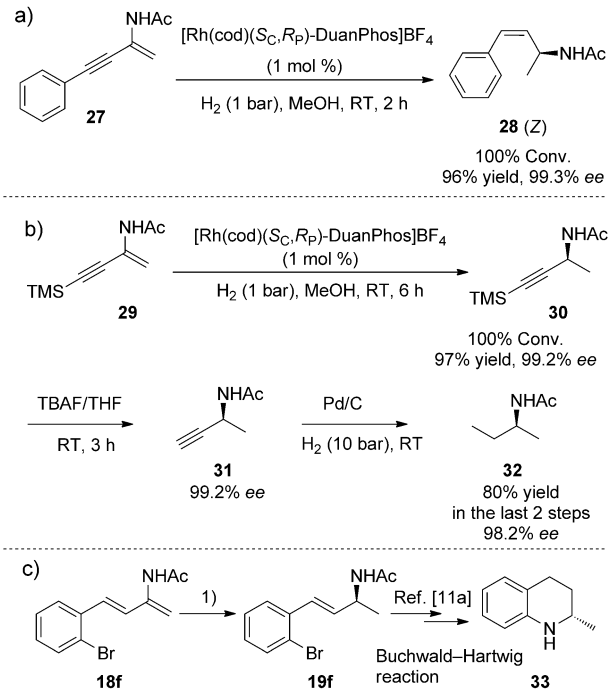




[a] Reaction conditions: **18** (0.1 mmol), **21** (0.001 mmol), MeOH (1 mL) under 1 bar H_2 for 2 h. Yields of isolated products are given. The enantioselectivities were determined by HPLC using a chiral stationary phase.

(**18q**) all led to chiral 4-alkyl allylic amines in full conversion and with up to 99% *ee* (Table 2, entries 15–17). A slightly lower *ee* value has been observed with substrate **18r** (Table 2, entry 18).

To expand the substrate scope of enamides, we have also prepared an enamide bearing an alkyne moiety. The asymmetric hydrogenation of *N*-(4-phenylbut-1-en-3-yn-2-yl)acetamide (**27**) by using the [Rh(cod)(S_C,R_P)-DuanPhos]BF_4 complex as the catalytic system surprisingly did not lead to the corresponding *N*-(4-phenylbut-3-yn-2-yl)acetamide, but offered (*Z*)-*N*-(4-phenylbut-3-en-2-yl)acetamide (**28**) as the hydrogenation product with full conversion and an excellent *ee* value (99% *ee*; Scheme 3a). To our knowledge, this is the first synthesis of *Z*-allylic amine derivates through an asymmetric hydrogenation method (Scheme 3a). However, the hydrogenation of **29** offered **30** with high *ee* values and



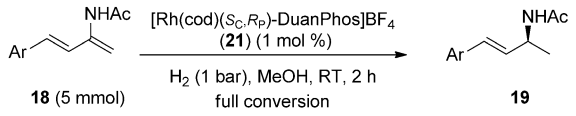
Scheme 3. a) Synthesis of *Z*-allyllic amine **28**. b) Synthesis of (*S*)-but-3-yn-2-amine **31** and (*S*)-butan-2-amine **32**. TMS = trimethylsilyl, TBAF = tetrabutylammonium fluoride. c) Catalytic enantioselective synthesis of 2-methyl-1,2,3,4-tetrahydro-quinoline (**33**) starting from **19f**. Reaction conditions: 1) [Rh(cod)(S_C, R_P)-DuanPhos]BF_4, 1 bar H_2, MeOH, RT, 2 h.

high yield and the alkyne group stayed untouched (Scheme 3b). Therefore, a key chiral intermediate such as **6** and its enantiomer **31** can be efficiently prepared.

Removal of the TMS group from **30** generates the useful chiral building block **31**, which can be used for producing the drugs **11**[2d] and **14**[2g] (Scheme 1) through a Sonogashira coupling. Importantly, we have prepared simple aliphatic amines such as the chiral 2-aminobutane **32** and its derivative in high yields and enantioselectivities (Scheme 3b). These simple chiral aliphatic amines are useful building blocks for producing drugs and drug candidates such as **9**[2b] and **13**.[2f] To our knowledge, this is the first report addressing the synthesis of **32** through asymmetric hydrogenation reaction.

The hydrogenation was also performed on a large scale to test its practicality (Scheme 4). When the reaction was conducted at 5 mmol, allylic amines **19a**, **19f**, and **19h** could be prepared in high yields with full conversion and high enantioselectivities (98–99% *ee*).

To further demonstrate the potential of this simple and highly efficient catalytic asymmetric hydrogenation method, we prepared key intermediates for the synthesis of several bioactive active compounds. The 2-methyl-1,2,3,4-tetrahydroquinolines are ubiquitous in many naturally occurring alkaloids and related biologically active molecules, and this motif exists in many pharmaceutical products. Product **19f** was used for the preparation of 2-methyl-1,2,3,4-tetrahydroquinolines by using the Buchwald–Hartwig amination reaction.[11] The hydrogenation of dienamide **18f** gave direct access to **19f** with >99% *ee* and full conversion (Scheme 3c). This trans-



19a, Ar = Ph, 0.92 g, 97% yield, 99% *ee*
19f, Ar = *o*-BrC_6H_4, 1.20 g, 90% yield, 99% *ee*
19h, Ar = *p*-MeC_6H_4, 0.95 g, 94% yield, 98% *ee*

Scheme 4. Gram-scale reaction for the preparation of the enantiomerically enriched allylic amine **19**.

formation is efficient in the preparation of the corresponding chiral aliphatic amines.

In summary, we have developed a Rh-catalyzed asymmetric hydrogenation to synthesize chiral aliphatic amines such as allylic amines and their derivatives. Notably, full conversion and excellent enantioselectivities were obtained in the hydrogenations of (*E*)-*N*-(buta-1,3-dien-2-yl)acetamides. A chiral *Z*-allylic amine was obtained for the first time through an Rh–DuanPhos catalyzed asymmetric hydrogenation. The general method for preparing chiral aliphatic amines should have a broad impact in synthesizing a number of chiral pharmaceutical products.

Experimental Section

General hydrogenation procedure: In a nitrogen-filled glovebox, the Rh complex (0.01 mmol) was dissolved in anhydrous MeOH (1.0 mL) and the solution was equally divided into 10 vials charged with dienamide substrates (0.1 mmol) in anhydrous MeOH solution (1.0 mL). The resulting vials were transferred to an autoclave, which was charged with 1 atm of H_2, and the reaction mixtures were stirred at room temperature for 2 h. The hydrogen gas was released slowly and the solution was concentrated and passed through a short column of silica gel to remove the metal complex. The chiral amines were then analyzed by using HPLC and GC on a chiral stationary phase to determine the enantiomeric excesses.

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