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Asymmetric Synthesis of C-Aliphatic Homoallylic Amines and Biologically Important Cyclohexenylamine Analogues

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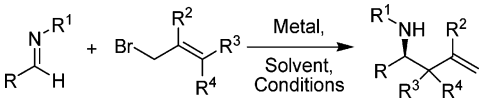
Abstract: An efficient method for the asymmetric synthesis of C-aliphatic homoallylic amines with up to 94% yield and 80% de is reported. Ring-closing metathesis of several chiral homoallylic amines using the second-generation Grubbs catalyst provided easy access to a wide variety of cyclohexenylamines.

The enantio- and diastereoselective construction of homoallylic amines[1] has become a significant goal in the field of medicinal chemistry and organic synthesis. Within the realm of biologically active compounds, the homoallylic amine functional array is an important structural subunit[2] and a key intermediate in the synthesis of alkaloid natural products and nitrogen heterocycles.[3] The development of new methods for the asymmetric synthesis of homoallylic amines is therefore of considerable importance.

Among the most frequently employed methods for accessing chiral homoallylic amines is the Barbier allylation[4] of chiral imines (Scheme 1). Although the metal-mediated allylation of C-aromatic imines has been very successful,[1,2] the development using C-aliphatic imines has been less explored. While innovative and notable advances have been documented,[5] a truly convenient and general method remains elusive.

Despite the emergence of the convenient Barbier-type allylation using indium metal, most of the effective examples documented mainly involve allyl bromide.[6] The search for an extension of this protocol to more complex

SCHEME 1. Barbier Allylation of Imines



allylic bromides, such as prenyl and cinnamyl, produced undesirable aldehyde products. For that reason, development of an efficient method for the assembly of chiral C-aliphatic amines in a stereocontrolled manner with a wider variety of allylic bromides is in high demand. Herein, we report an asymmetric synthesis of homoallylic amines via the zinc-mediated allylation of C-aliphatic imines using optically pure (*S*)-phenylglycine acid methyl ester as the chiral auxiliary,[7−11] which can subsequently be removed with ease.[12]

Our initial studies revealed that relatively high asymmetric induction can be accomplished using a variety of allylic bromides (Table 1). When cyclohexanecarboxaldehyde was used as the corresponding aldehyde moiety for the construction of chiral imine **1a**, the reactions with allylic bromides generally provided satisfactory to excellent yields. In fact, crotylation and prenylation of chiral imine **1a** provided excellent yields with good selectivities and syn:anti ratios (Table 1, entries 1 and 2). As expected, this Zn-mediated allylation using THF as the solvent of choice gave the desired homoallylic amines derived from 3-phenylpropanal, though in modest yields, except when prenyl and cinnamyl bromides were used (Table 1, entries 5 and 6). Nonetheless, good diastereoselectivities and syn:anti ratios were achieved in all cases.

When this methodology was expanded to 4-pentenal and *cis*-hept-4-enal (imines **1c** and **1d**, respectively), considerable variation of allylic bromides is possible without any significant loss in efficiency of diastereocontrol (up to 92% yield and 80% de). A relatively high ratio of syn adducts was obtained in all cases. Prenyl bromide proved again to be the allylic bromide of choice as it gave the desired chiral homoallylic amine with excellent yields and impressive diastereoselectivities (Table 1, entries 8 and 11). It is interesting to note that the reactions of cinnamyl bromide with chiral imines **1a** and **1b** produced

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(12) The removal of the (*S*)-phenylglycine acid methyl ester chiral auxiliary has been achieved in an overall yield of 89% from two steps (reduction of the ester moiety using DIBAL-H and a subsequent oxidative cleavage using $Pb(OAc)_4$).

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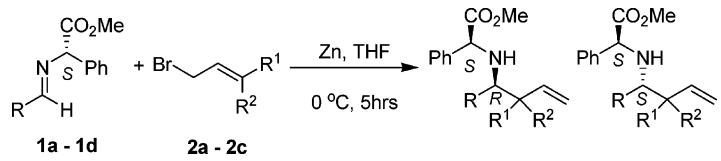
TABLE 1. Zn-Mediated Allylation of Chiral Imines 1 Using Different Allylic Bromides 2[a,b]



1a - 1d 2a - 2c

entry	imine	R	homoallylic amine	R^1	R^2	yield (%)	dr (*S*,*R*:*S*,*S*)[c]	syn:anti[d]
1	**1a**	*c*-C_6H_5	**3a**	Me	H	94	80:20	75:25[e]
2	**1a**	*c*-C_6H_5	**3b**	Me	Me	92	89:11	
3	**1a**	*c*-C_6H_5	**3c**	Ph	H	65	88:12	82:18[f]
4	**1b**	$Ph(CH_2)_2$	**4a**	Me	H	39	78:22	79:21[e]
5	**1b**	$Ph(CH_2)_2$	**4b**	Me	Me	72	89:11	
6	**1b**	$Ph(CH_2)_2$	**4c**	Ph	H	58	88:12	90:10[f]
7	**1c**	$CH_2{=}CH(CH_2)_2$	**5a**	Me	H	59	75:25	86:14[e]
8	**1c**	$CH_2{=}CH(CH_2)_2$	**5b**	Me	Me	72	89:11	
9	**1c**	$CH_2{=}CH(CH_2)_2$	**5c**	Ph	H	62	90:10	95:5[e]
10	**1d**	$CH_3CH_2CH{=}CH(CH_2)_2$	**6a**	Me	H	53	80:20	81:19[e]
11	**1d**	$CH_3CH_2CH{=}CH(CH_2)_2$	**6b**	Me	Me	92	90:10	
12	**1d**	$CH_3CH_2CH{=}CH(CH_2)_2$	**6c**	Ph	H	67	90:10	88:12[e]

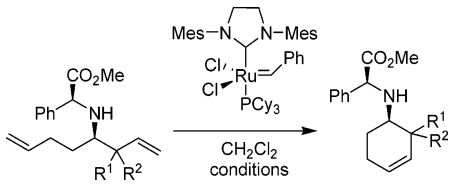
[a] The reactions were performed in THF (5 mL) with 1 mmol of chiral imine by using excess Zn (3.2 mmol) and allylic bromide (3.0 mmol). [b] Allylic bromides used (crotyl and cinnamyl) were predominantly trans. [c] Determined by ^{1}H NMR and ^{13}C NMR, except in some cases where the diastereomers can be well separated by flash column chromatography. [d] Determined by ^{1}H NMR and ^{13}C NMR; syn:anti ratios refer to only the major diastereomer (*S*,*R*). [e] No linear homoallylic amine was observed. [f] Traces of linear homoallylic amines were isolated.

trace amounts of the linear homoallylic amine adducts formed. When the same bromide was injected into either chiral imines **1c** or **1d**, no such side products were observed.[6c]

To illustrate the synthetic potential of our methodology, homoallylic amines (**5a**−**c**), synthesized from **1c**, were converted to the corresponding cyclohexenylamines[13] using a ring-closing metathesis approach.[14] These chiral cyclohexenylamines are important building blocks for several alkaloids, such as sarain A,[15] aphanorphine,[16] hetisine,[17] and some of the *Securinega* group.[18] More interestingly, some of these cyclohexenylamines, in the presence of inorganic pyrophosphate, have been reported to show strong cooperative inhibition with trichodiene synthase.[19]

As revealed in Table 2, the homoallylic amines underwent ring-closing metathesis to afford excellent yields.[20]

TABLE 2. Ring-Closing Metathesis[a] of Homoallylic Amines 5a−c



entry	homoallylic amine	R^1	R^2	*T* (°C)	time (h)	product	yield (%)
1	**5a**	Me	H	40[b]	6	**7a**	84
2	**5b**	Me	Me	25	12	**7b**	92
3	**5c**	Ph	H	40[b]	6	**7c**	86

[a] The reactions were performed in CH_2Cl_2 (10 mL) with 0.1 mmol of chiral homoallylic amine by using 0.01 mmol of Grubbs' second-generation catalyst, unless otherwise stated. [b] Reactions were reflux at 40 °C if the TLC showed starting material after 12 h of stirring at room temperature.

These ring-closing reactions were performed by stirring a dichloromethane solution of the homoallylic amines in the presence of 10 mol % Grubbs' second-generation catalyst for up to 12 h. In all cases, the cyclohexenylamine derivatives can be obtained in very good yields.[21] It is important to note that most of the homoallylic amines needed reflux conditions to allow their full depletion (Table 2, entries 1 and 3). Notably, homoallylic amine **5b** afforded the desired product **7b** in excellent yield (92%) with 10 mol % catalyst when the mixture was stirred at ambient temperature.

Dibromo adduct **8** was synthesized according to Scheme 2, and on the basis of its X-ray crystallographic analysis (Figure 1),[22] the absolute configuration of the major

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(20) Only the major (*S*,*R*)-diastereomer was allowed to undergo ring-closing metathesis.

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(22) Only pure isomer **7c** was used to synthesize **8**, and the latter was obtained as a single isomer based on ^{1}H NMR and ^{13}C NMR analyses.

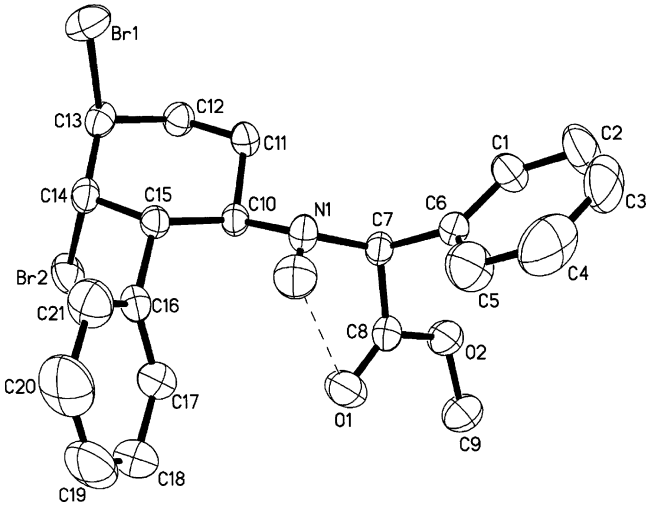
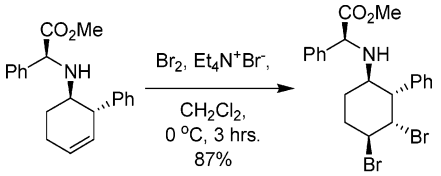


FIGURE 1. X-ray structure of **8**.

SCHEME 2. Dibromination of Cyclohexenylamine 7c



7c **8**

homoallylic amine diastereomers can therefore be established as (*S*,*R*). By simply employing a retrosynthetic study, we recognized the major homoallylic amine diastereomer with a substituent (methyl or phenyl group) at the γ-position as the syn adduct.

In summary, we have successfully described an efficient allylation of chiral C-aliphatic imines, affording the desired aliphatic homoallylic amines in high diastereoselectivities. This methodology enabled the preparation of a larger variety of chiral C-aliphatic homoallylic amines, including those inaccessible by conventional systems. By analyzing the X-ray crystallographic data of **8**, we are able to establish the absolute configuration of the homoallylic amines obtained. Importantly, the syn and anti isomers can be unambiguously established. The simple synthesis of biologically important cyclohexenylamines by the ring-closing metathesis reaction has also been demonstrated. This course offers a valuable alternative to the Diels−Alder strategy to cyclohexenes with an electon-donating substituent in the homoallylic position. The combination of the ring-closing metathesis reaction with transannular cyclization should provide access to interesting natural products.

Experimental Section

General Procedure for the Preparation of Imines 1. To a stirred solution of aldehyde (1 mmol, 1 equiv) and Na_2SO_4 (0.5 g) in dichloromethane (3 mL, 0.33 M) under nitrogen at 0 °C was added (*S*)-phenylglycine methyl ester (1.5−2.0 mmol, 1.5−2.0 equiv). The reaction mixture was stirred for 5 h. The resulting reaction mixture was then filtered and concentrated in vacuo. The crude product obtained was used without purification for subsequent steps.

General Procedure for the Preparation of Homoallylic Amines 3−6. To a stirred suspension of the chiral imine (1 mmol) in THF (5 mL) and "activated" Zn powder (3.2 mmol) was added the allylic bromide (3.0 mmol) at 0 °C, and the mixture was stirred for up to 7 h. The reaction mixture was then quenched with saturated $NaHCO_3$ (10 mL) before being extracted with CH_2Cl_2 (3 × 10 mL). The mixture was then washed with water (2 × 10 mL) before being dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by flash column chromatography.

General Procedure for the Preparation of Cyclohexenylamines 7. To a stirred suspension of the chiral homoallylic amine (1 mmol) in CH_2Cl_2 (100 mL) was added Grubbs' second-generation catalyst (0.1 mmol) in two portions (interval of 30 min) at 25 °C, and the mixture was stirred for up to 12 h. Reactions were reflux at 40 °C if the TLC showed the starting material after 12 h of stirring at room temperature. The reaction mixture was then filtered through a pad of Celite before being concentrated in vacuo. The crude product was purified by flash column chromatography.

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Supporting Information Available: Experimental details and characterization data for the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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