A Highly Practical Approach to Chiral Homoallylic-homopropargylic Amines via *aza*-Barbier Reaction

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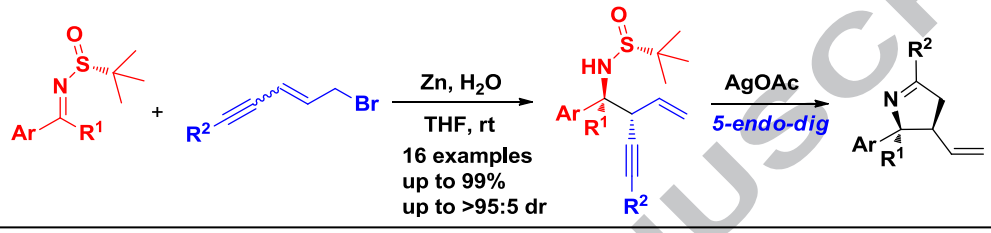

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A Highly Practical Approach to Chiral Homoallylic-homopropargylic Amines via *aza*-Barbier Reaction

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ABSTRACT

The first access to chiral homoallylic-homopropargylic amine bearing two contiguous stereocentes has been well accomplished *via* zinc-promoted *aza*-Barbier reaction. *N-tert*-Butanesulfinyl ketimines are well-tolerated substrates, providing the tertiary amines in high yields and with excellent diastereoselectivities. 3,4-Dihydro-2*H*-pyrroles could be prepared in high efficiency by cyclization of the corresponding amines.

Homopropargylic amines are widely utilized in the construction of natural products,[1] pharmaceutical molecules and a wide range of heterocyclic compounds, such as pyrrolines,[2,3] pyrroles, [4] piperidines,[5] tetrahydropyridines,[6] and other chemicals.[7] Pyrrolines are especially critical intermediates in pharmaceutical industry since they can be conveniently transformed to pyrroles and pyrrolidines. Accordingly, asymmetric synthesis of homopropargylic amines has attracted considerable attention in recent years.[8] In these advancements, addition of nucleophilic reagents to imines has been demonstrated as an elegant approach. Nucleophilic reagents include allenylborane,[9] allenylzinc,[10] allenyltin,[11] allenylsilane,[12] propargyl bromide,[13] silylated propargyl bromide,[14] etc.[15] However, in most cases, the use of unstable nucleophilic reagents or the formation of allene byproducts simultaneously in progargylation limits their applications. On the other hand, to the best of our knowledge, there is rare approach for the preparation of enantioenriched homopropargylic amine bearing two contiguous stereocenters in one-pot fashion to date. Therefore, developing new method to build enantioenriched homopropargylic amines, especially for tertiary amines containing two vicinal stereocenters, is still in high demand.

N-tert-Butanesulfinyl imines can provide unique reactivity and stereoselectivity in various reactions and prove to be extremely versatile chiral reagents.[16] Our group has made continuing efforts in the asymmetric synthesis of various amines using this chiral reagent in past several years.[17] We have found that various allylzinc reagents or allylindium reagents formed *in situ* could react with *N-tert*-butanesulfinyl imines via *aza*-Barbier reaction leading to a diversity of homoallylic amines. For example, remarkable controlled stereoselectivity reversal was achieved in Zn-promoted allylation of *N-tert*-butanesulfinyl imines by simply changing the solvent.[17a] Futhermore, it is worth noting that we also reported an asymmetric propargylation of *N-tert*-butanesulfinyl ketimines using 3-bromo-1-trimethylsilyl-1-propyne to generate chiral quaternary stereocenter-containing homopropargylic amines in good yields and with excellent diastereoselectivities (Scheme 1a).[17g] Based on our previous studies, here we report a novel method to synthesize homopropargylic amines bearing two contiguous stereocenters and homoallylic units.

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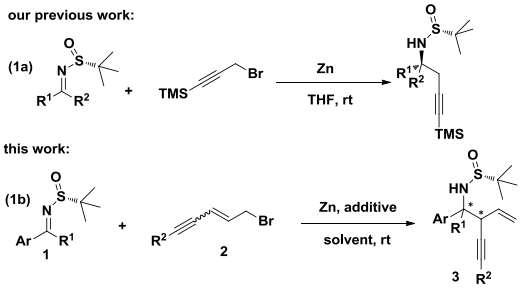
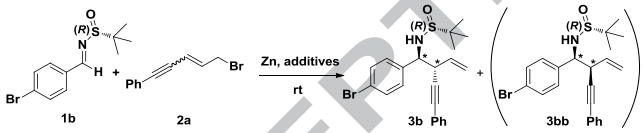


Scheme 1. Asymmetric construction of homoallylic-homopropargylic amines

We contrived to utilize *γ*-ethynl substituted allylic bromide **2** as the allylic reagent to react with *N-tert*-butanesulfinyl imines to afford homopropargylic amines, while vinyl groups are introduced as well (Scheme 1b).

We preliminarily utilized *γ*-phenylethynl allylic bromide **2a** and *N-tert*-butanesulfinyl imine **1b** to examine the reaction. **2a** could be easily prepared from methyl propiolate in 40% overall yield (*Z*/*E* 12:1) over four steps[18]. As shown in table 1, the reaction proceeded smoothly in the presence of 2 equiv of zinc powder with *γ*-phenylethynl allylic bromide **2a** and afford the desired products in high yield (99%) but with poor diastereoselectivity (75:25) under argon at room temperature. The similar result was observed by reducing the amount of **2a** to 1.5 equiv (Table 1, entries 1 and 2). When the amount of **2a** was reduced to 1.1 equiv, dr increased to 80:20 with the decrease of yield to 82% (entry 3). Changing the solvent to DMF or adding LiCl did not influence the result positively (entries 4 and 5). According to our previous work,[17a,17d,17e,17g] the content of water could have a subtle impact on both yield and diastereoselectivity of the *aza*-Barbier-type allylation. Therefore, we subsequently screened the effect with regard to the amount of water.

Table 1. Screening and optimization of the reaction conditions

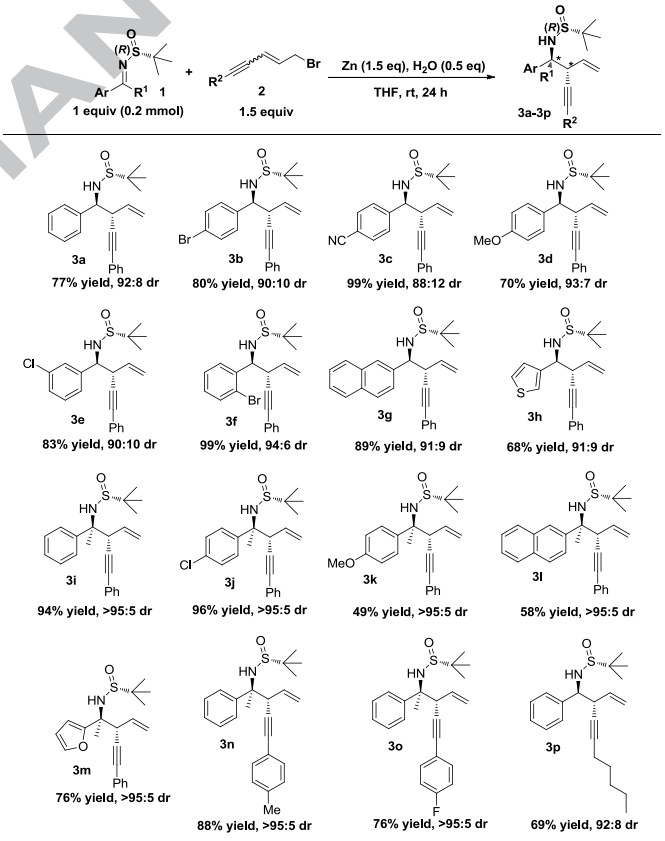


Entry[a]	T (°C)	Zn/**2a** (eq)	H_2O (eq)	Yield (%)[b]	dr[c]
1	rt	2.0	-	99	75:25
2	rt	1.5	-	99	74:26
3	rt	1.1	-	82	80:20
4[d]	rt	1.1	-	72	complex
5[e]	rt	2.0	1.0	64	65:35
6	rt	1.1	2.0	48	90:10
7	rt	1.1	1.0	56	90:10
8	rt	1.1	0.5	67	90:10
9[f]	rt	1.1	0.5	51	91:9
10	0	1.1	0.5	47	92:8
11	-20	1.1	0.5	26	93:7
12[g]	rt	1.1	0.5	37	complex
13	**rt**	**1.5**	**0.5**	**80**	**90:10**
14	rt	2.0	0.5	82	90:10

[a] Reaction was performed with imine **1b** (0.20 mmol) and Zn/**2a** in 4 mL THF for 24 hours unless otherwise noted. [b] Isolated yield. [c] Determined by ^{1}H NMR and LC-MS of the crude products. [d] DMF as solvent. [e] 4 mL of DMF was used as solvent and 2 equiv of LiCl was added. [f] 8 mL of THF as solvent. [g] 2 equiv of LiCl was added.

Better diastereoselectivity (90:10) was observed when 0.5 to 2.0 equiv of water was added and 0.5 equiv of water afforded the best yield (67%) (entries 6-8). Although reducing temperature and concentration improved diastereoselectivity slightly, obvious decrease of the yield were observed (entry 9-11). Besides, the presence of LiCl in THF solvent only complicated the reaction (entry 12). Whereafter, we increased the amount of zinc and allylic bromide reagent **2a** in order to get higher yield (entries 13 and 14). Finally, we selected entry 13 as the optimized reaction conditions (80%, dr 90:10).

With the optimized conditions in hand, we turned our attention to the substrate scope and generality of the reaction. As summarized in scheme 2, a wide range of (*R*)-*N-tert*-butanesulfinyl imines **1** were examined to react with *γ*-ethynl allylic bromide **2** in the presence of zinc powder and water in THF at room temperature.



Scheme 2. Asymmetric synthesis of homoallylic-homopropargylic amines

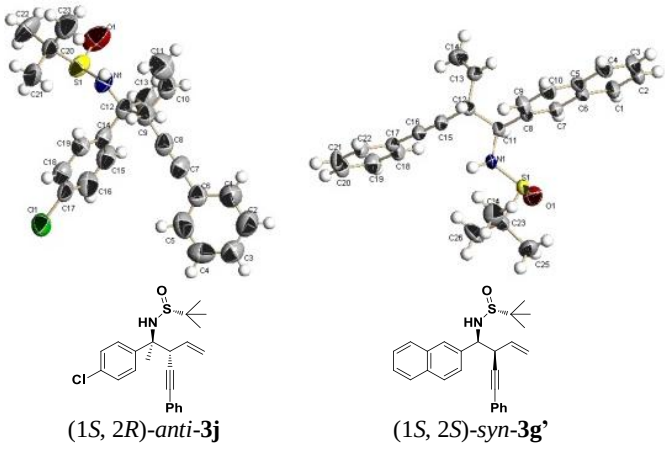
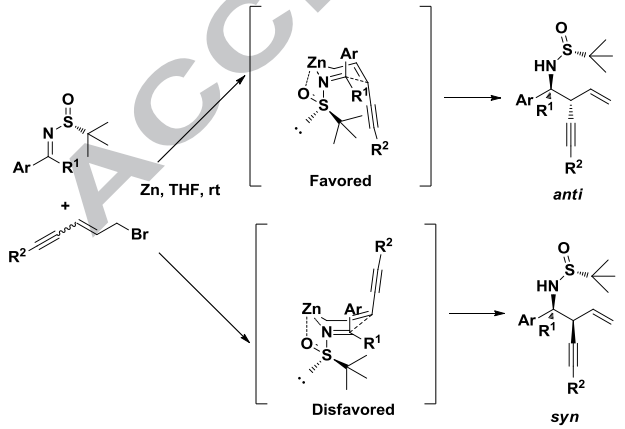


Figure 1. X-ray crystal structure of (1*S*, 2*R*)-*anti*-**3j** and (1*S*, 2*S*)-*syn*-**3g'**

To our delight, all the reactions went smoothly and afforded the desired homoallylic-homopropargylic amines in good to excellent yields and with good to excellent diastereoselectivities (Scheme 2). For aldimines, we found that position and electronic property of substituent on the aryl-ring did not significantly affect either reactivity or selectivity of the reaction (3a-3h). Notably, ketimine substrates, including naphthalenyl methyl and furyl methyl ketimines, were competent to approach excellent diastereoselectivities (>95:5 dr) (3i-3m). Besides, methyl and fluorine atom on the benzene ring of allylation reagent **2** were well tolerated (3n and 3o). Pleasingly, *γ*-heptynl allylic bromide reacting with aldimine **1a** also afforded corresponding amine **3p**, which made this method more versatile (3p). Unfortunately, aliphatic sulfinyl imines could only give poor diastereoselectivity.

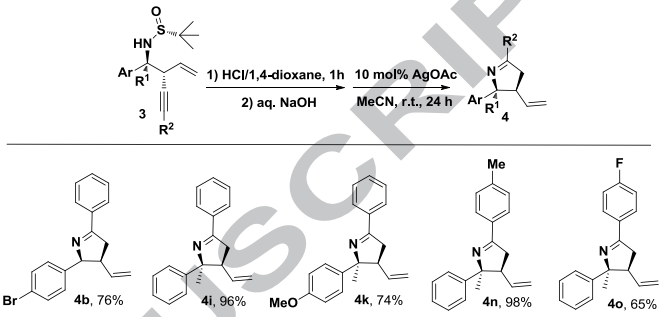
The absolute structures of obtained products were identified unambiguously through X-ray crystallography of **3j**[19a] and **3g'**[19b] (the minor product in reaction for 3g) (Figure 1).

The outcome of stereochemistry of the products were consistent with the transition state model proposed previously.[17e] A six-membered cyclic chair-form transition state model is preferred wherein zinc is presumed to coordinate both to the imine nitrogen and the sulfinyl oxygen. Compared to chair-form transition, boat-form transition is obviously unfavored because of the steric repulsion between the ethynyl group and the imine aryl group (Scheme 3).



Scheme 3. Possible mechanism of reaction stereocontrol

With the enantioenriched homoallylic-homopropargylic amines in hand, we investigate the transformations of enantiopure homopropargylic amines to prepare chiral substituted-pyrroles. Unfortunately, the desired 2,3-dihydro-1*H*-pyrrole derivatives cannot be generated by treatment of homoallylic-homopropargylic amine **3a** with several different Lewis acids. Then, the *tert*-butanesulfinyl group was removed by 2 mol/L HCl in dioxane in nearly quantitative yield. After alkalization, the free amines were subjected to 10 mol% AgOAc in MeCN at room temperature. A series of 3,4-dihydro-2*H*-pyrrole derivatives **4b**, **4i**, **4k**, **4n** and **4o** were obtained successfully *via* 5-*endo-dig* cyclization and subsequent isomerization from initially produced enamines to imines, which were accordant with the previous reports by other groups[3] (Scheme 4).



Scheme 4. Synthesis of 3,4-dihydro-2*H*-pyrrole derivatives

In conclusion, we have developed a Zn-promoted *aza*-Barbier-type reaction to asymmetric synthesis of a broad spectrum of homoallylic-homopropargylic amines bearing two contiguous stereocenters using *γ*-ethynyl allylic bromide as allylation reagent in mild conditions. It is notable that *N*-tert-butanesulfinyl ketimines are outstandingly amenable to this approach. Besides, cyclization of deprotected homopropargylic amines can afford 3,4-dihydro-2H-pyrrole derivatives, which are believed to be useful building blocks in the synthesis of some bioactive compounds.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at

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19. (a) CCDC 1021881 contains the crystallographic data for **3j**; (b) CCDC 1021880 contains the crystallographic data for **3g'**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Highlights

A Highly Practical Approach to Chiral Homoallylic-homopropargylic Amines via *aza*-Barbier Reaction

Bin-Hua Yuan, Zhi-Cheng Zhang, Wen-Jie Liu, and Xing-Wen Sun*

- The first access to chiral homoallylic-homopropargylic amine bearing two contiguous stereocentes.
- A novel allylic bromide was illustrated in *aza*-Barbier reaction.
- Enantioenriched 3,4-dihydro-2H-pyrroles was prepared in high efficiency via *5-indo-dig* pathway.

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