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# Synthesis of Chiral Propargylamines, Chiral 1,2-Dihydronaphtho[2,1-b]furans and Naphtho[2,1-b]furans with C-Alkynyl N,N'-Di-(tert-Butoxycarbonyl)-Aminals and β-Naphthols

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Supporting information for this article is given via a link at the end of the document.

**Abstract:** Chiral phosphoric acid-catalyzed couplings of *C*-alkynyl *N*,*N'*-di-(*tert*-butoxycarbonyl)-aminals with  $\beta$ -naphthols led to chiral propargylamines in moderate to high yields with high to excellent enantioselectivity, in which the reactions underwent sequential chiral phosphoric acid-catalyzed *in situ* formation of *N*-(*tert*-butoxycarbonyl)-imines (*N*-Boc-imines) from the aminals, and 1,2-addition of  $\beta$ -naphthols to the *N*-Boc-imines. Chiral 1,2-dihydronaphtho[2,1-*b*]furans and naphtho[2,1-*b*]furans were prepared with the satisfactory results when 10 mol% AgOAc and 20 mol% 2,6-lutidine or 1.2 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were added to the resulting chiral propargylamines solution, respectively.

#### Introduction

Propargylamines are one kind of important synthetic intermediates and versatile building blocks<sup>[1]</sup> for the synthesis of diverse amine derivatives<sup>[2]</sup> as well as natural products<sup>[3]</sup> and biologically active molecules.<sup>[4]</sup> Chiral propargylamines are key precursors for the synthesis of pharmaceutical molecules.<sup>[5]</sup> The reactions with propargylamines as the substrates can provide miscellaneous heterocyclic compounds<sup>[6]</sup> such as pyrroles,<sup>[7]</sup> pyrrolines,<sup>[8]</sup> pyrrolidine,<sup>[9]</sup> pyrazines,<sup>[10]</sup> pyrazoles,<sup>[11]</sup> pyridines,<sup>[12]</sup> dihydropyridines,<sup>[13]</sup> isoxazoles,<sup>[14]</sup> oxazolidines,<sup>[15]</sup> thiazoles<sup>[16]</sup> and thiazolidines.<sup>[17]</sup> The common methods for synthesis of chiral propargylamines include the asymmetric alkynylation of imines<sup>[18,19]</sup> and the catalytic asymmetric addition of nucleophiles to previously prepared<sup>[20]</sup> or in situ generated<sup>[21,22]</sup> C-alkynyl imines (Scheme 1a). In 2016, Shao and co-workers reported the catalytic asymmetric arylations of C-alkynyl imines leading to chiral propargylamines with C-alkynyl N-Boc-protected N,Oacetals and phenols as the substrates.<sup>[23]</sup> Benzofurans and naphthofurans are the important class of O-heterocyclic compounds with various biological and pharmacological activities.<sup>[24-26]</sup> The naphthofuran moiety is used as the privileged structure<sup>[27]</sup> in the discovery of anticancer agents<sup>[24a]</sup> and regulators of the nuclear receptors HNFa7.<sup>[28]</sup> Several methods for the synthesis of naphthofurans have been developed because of importance of naphthofurans in pharmaceutical chemistry.<sup>[29]</sup> Dihydrobenzofurans that widely occur in the synthetic molecules and natural products possess various biological activities.[30]

a) propargylamines b) OMe он ÒΜe ÓМе с OH A megapodiol (2R.3S)-3'.4'-di-O-methylcedrusin callislignan A п сно G MeO Е annullatin A Phalarin HС

For example, megapodiol (A) is an antileukemic agent,<sup>[31]</sup>

neolignan callislignan A (B) exhibits



**Scheme 1.** a) Previous routes for synthesis of chiral propargylamines. b) The representative examples of dihydrobenzofurans and dihydronaphtho[2,1-*b*]furans with various biological activities. c) Our strategy for synthesis of chiral propargylamines, chiral 1,2-dihydronaphtho[2,1-*b*]furans and naphtho[2,1-*b*]furans.

antibacterial activity against Staphylococcus aureus,<sup>[32]</sup> (*2R*,*3S*)-3,4'-di-O-methylcedrusin (**C**) is an antitumor neolignan,<sup>[33]</sup> and annullatin A (**D**) isolated from Cordyceps annullata shows the potent agonistic activity toward the cannabinoid receptors CB1 and CB2 (Scheme 1b).<sup>[34]</sup> Particularly, 3-amino-2,3dihydrobenzofurans are of great importance in drug discovery. For example, phalarine (**E**) isolated from Phalaris coerulescens

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shows high structural diversity and a broad bioactivity profile,<sup>[35]</sup> and compound F is an important cell motility inhibitor (Scheme 1b).[36] In the past decade years, several methods for enantioselective synthesis of 3-amino-2,3-dihydrobenzofurans have been developed.[37] 1,2-Dihydronaphtho[2,1-b]furans play a key role in medicinal chemistry for their diverse pharmacological activities such as antiinflammatory activity (G), melatonin receptor ligands (H), α-chymotrypsin inhibitor (I), C<sub>17,20</sub>-lyase inhibitor (J) and 5-lypoxygenase inhibitor (K).  $^{\rm [38]}$  However, enantioselective synthesis of 1,2-dihydronaphtho[2,1-b]furans, especially 1amino-1,2-dihydronaphtho[2,1-b]furans is rare. Herein, we report synthesis of chiral propargylamines, chiral 1,2dihydronaphtho[2,1-b]furans and naphtho[2,1-b]furans with Calkynyl N,N'-di-(tert-butoxycarbonyl)-aminals and  $\beta$ -naphthols (Scheme 1c).

#### **Results and Discussion**

Optimization of conditions for the synthesis of chiral propargylamines



Entry	CPA	additive	t (h)	yield (%) <sup>[b]</sup>	ee (%) <sup>[c]</sup>
1	( <i>R</i> )- <b>C1</b>		10	78	59
2	( <i>R</i> )- <b>C2</b>		10	74	74
3	( <i>R</i> )- <b>C3</b>		10	80	38
4	( <i>R</i> )- <b>C4</b>		10	79	19
5	( <i>R</i> )- <b>C5</b>		10	81	18
6	( <i>R</i> )- <b>C6</b>		10	64	52
7	( <i>R</i> )- <b>C7</b>		10	80	3
8	( <i>R</i> )- <b>C8</b>		10	77	16
9	( <i>R</i> )- <b>C9</b>		10	76	87
10	( <i>R</i> )- <b>C9</b>	Mg <sub>2</sub> SO <sub>4</sub>	10	83	70
11	( <i>R</i> )- <b>C9</b>	Na <sub>2</sub> SO <sub>4</sub>	10	78	90
12	( <i>R</i> )- <b>C9</b>	3 Å MS	10	41	80
13	( <i>R</i> )- <b>C9</b>	Na <sub>2</sub> SO <sub>4</sub>	10	62	90
14	( <i>R</i> )- <b>C9</b>	Na <sub>2</sub> SO <sub>4</sub>	10	82	87
15	( <i>R</i> )- <b>C9</b>	Na <sub>2</sub> SO <sub>4</sub>	8	66	91
16	( <i>R</i> )- <b>C9</b>	Na <sub>2</sub> SO <sub>4</sub>	12	77	92
17	( <i>R</i> )- <b>C9</b>	$Na_2SO_4$	14	77	92
18	( <i>R</i> )- <b>C9</b>	Na <sub>2</sub> SO <sub>4</sub>	12	67	80
19	( <i>R</i> )- <b>C9</b>	Na <sub>2</sub> SO <sub>4</sub>	12	77	93
20	( <i>R</i> )- <b>C9</b>	Na <sub>2</sub> SO <sub>4</sub>	12	75	91

[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.1 mmol, 1.0 equiv), CPA ((*R*)-**C1**~(*R*)-**C9**) (5 µmol, 5 mol%), toluene (2.0 mL), temperature (60 °C), time (8-14 h) in a sealed Schlenk tube without extrusion of air. [b] Isolated yield. [c] The ee values were determined by HPLC analysis on a chiral stationary phase

using a Daicel Chiralpak OD-H column. [d] 50 °C. [e] 70 °C. [f] 1 mL of toluene. [g] 3 mL of toluene. [h] 4 mL of toluene.

Initially, di-tert-butyl (3-phenylprop-2-yne-1,1-diyl)dicarbamate (1a) and  $\beta$ -naphthalen-2-ol (2a) were used as the substrates to optimize reaction conditions including chiral phosphoric acids, additives, solvents, temperature and time. As shown in Table 1, nine chiral phosphoric acids (5 mol% relative to 1a and 2a) were first screened in 2 mL of toluene at 60 °C for 10 h (entries 1-9), and (R)-C9 gave the highest enantioselectivity (87% ee) and the higher yield (76%). Three anhydrous additives, MgSO<sub>4</sub>, Na<sub>2</sub>SO<sub>4</sub> and 3 Å MS, were attempted (entries 10-12), and Na<sub>2</sub>SO<sub>4</sub> provided 90% ee value (entry 11). We investigated the affection of reaction temperature and time (compare entries 9, 13-17), and found that 60 °C and 12 h were suitable (entry 16). Other solvents were attempted, and the results showed that toluene was optimal (see Table S1). Different volume of toluene was surveyed (entries 18-20), and 3 mL of toluene was suitable (entry 19). It should be pointed out that absolute configuration of 3a was determined by comparing structure of (R)-3q (absolute configuration of 3q was assigned to be (R)-form by X-ray diffraction analysis (see Supporting Information for details)).

#### Substrate scope for the synthesis of chiral propargylamines

#### Table 2. Synthesis of chiral propargylamines ((R)-3). [a]





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[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.1 mmol, 1.0 equiv), (*R*)-**C9** (5 µmol, 5 mol%), toluene (3.0 mL), temperature (60 °C), time (12 h) in a sealed Schlenk tube without extrusion of air. Isolated yield. The ee values were determined by HPLC analysis on a chiral stationary phase. Absolute configuration of **3q** was assigned to be (*R*)-form by X-ray diffraction analysis (see Supporting Information for details), and absolute configurations of products **3a** ~ **3p** and **3r** were determined by comparing structure of (*R*)-**3q**.

With the optimized conditions for synthesis of (R)-3 in hand, the substrate scope was surveyed for reactions of C-alkynyl N,N'-di-(tert-butoxycarbonyl)-aminals (1) and  $\beta$ -naphthols (2) under catalysis of (R)-C9 (Table 2). First, we investigated variation of R<sup>1</sup> subsituents in 1, and found that neutral ((R)-3a and (R)-3i, 77% and 67% yields with 93% and 96% ee, respectively), electrondonating ((R)-3b-3d, 64-80% yields with 90-96% ee), poor electron-withdrawing ((R)-3e-3g, 71-84% yields with 92% ee), strong electron-withdrawing ((R)-3h, 67% yield with 90% ee) groups were feasible. Subsequently, affection of R<sup>2</sup> subsituents in 2 was surveyed.  $\beta$ -naphthols (2) containing 6-Me ((R)-3j), 6-Br ((R)-3k), 7-p-tolyl ((R)-3l), 6-p-tolyl ((R)-3m), 6-naphthalen-1-yl ((R)-3n), 6-anthracen-9-yl ((R)-3o) and 6-phenanthren-9-y ((R)-3p) provided moderate to high yields (54-83%) with high to excellent ee values (86-94% ee). Finanlly, we attempted simultaneous variation of subsituents R<sup>1</sup> and R<sup>2</sup> in 1 and 2, and the couplings also afforded the satisfactory results ((R)-3q and (R)-3r, 60% and 53% yields with 94% and 91% ee, respectively).

# Optimization of conditions for one-pot two-step synthesis of chiral 1,2-dihydronaphtho[2,1-*b*]furans and naphtho[2,1-*b*]furans



[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.1 mmol, 1.0 equiv), (*R*)-**C9** (5  $\mu$ mol, 5 mol%), toluene (3.0 mL), temperature (60 °C), time (12 h) for the first step; temperature (30-70 °C), AgOAc (0.01 mmol, 0.1 equiv), base (0.02-

0.12 mmol, 0.2-1.2 equiv), time (20 min-2 h) for the second step. [b] Isolated yield. [c] The ee values were determined by HPLC analysis on a chiral stationary phase using a Daicel Chiralpak ID column. TEA = triethylamine. Py = pyridine. DMAP = 4-dimethylaminopyridine. Lut = 2,6-lutidine. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

Subsequently, we investigated one-pot two-step reactions of ditert-butyl (3-phenylprop-2-yne-1,1-diyl)dicarbamate (1a) and  $\beta$ naphthalen-2-ol (2a) including (R)-C9-catalyzed coupling of 1a and 2a to 3a, and cyclization of 3a under different conditions. The first-step reaction was performed under the optimal conditions of Table 2. Here, we surveyed the second-step reaction conditions including bases, catalysts, temperature and time (see Table S2-S4 for more details). As shown in Table 3, six bases (1.2 euiv) were added to the first-step resulting solution, respectively, and the reaction was conducted at 60 °C for 2 h. Surprisingly, only 4a (entry 5) or 5a (entry 6) was obsrved in the presence of 2,6lutidine or DBU, respectively. The yields of (S)-4a obviously increased when two silver salts were added the reaction solution, respectively (entries 7 and 8). We attempted variation of temperature and time, and found that 30 °C and 30 min were suitable for the formation of (S)-4a (entry 9). In addition, we also found that 70 °C was favorable for the synthesis of 5a (entry 10).

#### Substrate scope for the synthesis of chiral 1,2dihydronaphtho[2,1-*b*]furans and naphtho[2,1-*b*]furans





[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.1 mmol, 1.0 equiv), (*R*)-**C9** (5 µmol, 5 mol%), toluene (3.0 mL), temperature (60 °C), time (12 h) for the first step; AgOAc (0.01 mmol, 0.1 equiv), 2,6-lutidine (0.02 mmol, 0.2 equiv), temperature (30 °C), time (20 min) for the second step. Isolated yield. The ee values were determined by HPLC analysis on a chiral stationary phase. Absolute configuration of **4a** was assigned to be (*S*)-form by X-ray diffraction

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analysis (see Supporting Information for details), and absolute configurations of products  $4b \sim 4r$  were determined by comparing structure of (S)-4a.

After aetting the optimized conditions for the one-pot two-step reactions, we first surveyed substrate scope for synthesis of (S)-4. As shown in Table 4, the aminals (1) containing different substituents R1 on the aryl rings were amenable to this one-pot two-step reactions, and the formation of (S)-4 was not obviously affected by the substituents  $R^1$  including neutral ((S)-4a and (S)-4i, 80% yields with 93% and 98% ee, respectively), electrondonating ((S)-4b-4d, 67-75% yields with 91-93% ee), poor electron-withdrawing ((S)-4e-4g, 67-77% yields with 87-91% ee), strong electron-withdrawing ((S)-4h, 71% yield with 90% ee) groups. Next, various substituents  $R^2$  in **2** including 6-Me ((S)-4j), 6-Br ((S)-4k), 7-p-tolyl ((S)-4l), 6-p-tolyl ((S)-4m), 6-naphthalen-1yl ((S)-4n), 6-anthracen-9-yl ((S)-4o) and 6-phenanthren-9-y ((S)-**4p**) were attempted, and the corresponding  $\beta$ -naphthols (2) afforded moderate to high yields (58-75%) with high to excellent ee values (80-98% ee). We simultaneously changed subsituents  $R^1$  and  $R^2$  in 1 and 2, and the target products ((S)-4g and (S)-4r) were obtained in 56% and 57% yields with 87% and 85% ee, respectively. Subsequently, one-pot two-step synthesis of naphtho[2,1-b]furans (5) was investigated (Table 5). Similarly to Table 2 and Table 4, we tried respective and simultaneous variation of R<sup>1</sup> and R<sup>2</sup> in 1 and 2, and the target products (5a-5r) were successfully got in 59-88% yields.

Table 5. One-pot two-step synthesis of naphtho[2,1-b]furans (5).



[a] Reaction conditions: **1a** (0.1 mmol, 1.0 equiv), **2a** (0.1 mmol, 1.0 equiv), (*R*)-**C9** (5 µmol, 5 mol%), toluene (3.0 mL), temperature (60 °C), time (12 h) for the first step; DBU (0.12 mmol, 1.2 equiv), temperature (70 °C), time (2 h) for the second step. Isolated yield. Sructure of **5a** was determined by X-ray diffraction analysis (see Supporting Information for details).

#### **Reaction mechanism**

When (*S*)-4a was conducted at 70 °C for 2 h in the presence of 1.2 equiv of DBU, **5a** was obtained in 94% yield (Scheme 2a), which showed that the reactions underwent an intermediate 4 process during the formation of **5**. A possible mechanism for synthesis of (*R*)-3, (*S*)-4 and **5** is proposed in Scheme 2b based on our experimental results and previous references.<sup>[22]</sup> First, transformation of chiral phosphoric acid ((*R*)-**C9**)-catalyzed *C*-alkynyl *N*.*N'*-di-(Boc)-aminal (**1**) provides *C*-alkynyl *N*-Boc-imine (**1**'),<sup>[22a]</sup> and then treatment of (*R*)-**C9** with *in situ* generated **1'** and **2** through hydrogen bonds leads to coupling of **1'** and **2** giving (*R*)-**3**. Silver-catalyzed intramolecular cyclization of (*R*)-**3** provides (*S*)-**4** in the presence of 2,6-lutidine. Meanwhile, treatment of (*R*)-**3** in the presence of DBU undergoes a sequential two-step process including intramolecular cyclization of (*R*)-**3** to **4**, and isomerization of **4** to **5**.



**Scheme 2.** a) Transformation of (*S*)-4a to 5a in the presence of DBU. b) Possible mechanism for synthesis of (*R*)-3, (*S*)-4 and 5.

#### Scale synthesis and application of products



Scheme 3. a) Scale synthesis of (S)-4a. b) Scale synthesis of 5a. c) Application of 5a.

We attempted the scale synthesis of (S)-4a and 5a under the standard conditions (Scheme 3a, 3b), and the two products were prepared with the satisfactory results (81% yield and 90% ee for

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(S)-4a; 78% yield for 5a), which indicated that the present methods were very effective and practical for synthesis of chiral 1,2-dihydronaphtho[2,1-b]furans and naphtho[2,1-b]furans. Subsequently, we investigated application of 5a. Oxidation of 5a with SeO<sub>2</sub> in dioxane afforded 6 in 77% yield, and reduction of 6 with H<sub>2</sub> under catalysis of Pd/C gave 7 in 85% yield (Scheme 3c).

#### Conclusion

In summary, we have developed synthesis of chiral propargylamines, chiral 1,2-dihydronaphtho[2,1-b]furans and naphtho[2,1-b]furans using C-alkynyl N,N'-di-(tertbutoxycarbonyl)-aminals and  $\beta$ -naphthols as the substrates. For synthesis of chiral propargylamines, the reactions underwent sequential chiral phosphoric acid-catalyzed in situ formation of N-Boc-imines from the aminals, and 1,2-addition of  $\beta$ -naphthols to N-Boc-imines. The chiral propargylamines effectively and selectively transferred into chiral 1,2-dihydronaphtho[2,1-b]furans and naphtho[2,1-b]furans with the satisfactory results when 10 mol% AgOAc and 20 mol% 2,6-lutidine or 1.2 equiv of 1,8diazabicyclo[5.4.0]undec-7-ene (DBU) were added to the resulting solution, respectively. Therefore, the present methods provide a new strategy for synthesis of diverse molecules.

#### **Experimental Section**

Detailed experimental procedures, analytical data, NMR spectra, and HPLC traces are provided in the Supporting Information.

**Crystallographic data:** Deposition number 2045931 ((*R*)-3q), 2058506 ((*S*)-4a) and 2058504 (5a) contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre.

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#### **Conflict of interest**

The authors declare no conflict of interest.

**Keywords:** asymmetric synthesis • chiral phosphoric acid • chiral propargylamines • chiral dihydronaphtho[2,1-*b*]furans • naphtho[2,1-*b*]furans

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Synthesis of chiral propargylamines, chiral 1,2-dihydronaphtho[2,1-*b*]furans and naphtho[2,1-*b*]furans has been developed using *C*alkynyl *N*,*N*'-di-(*tert*-butoxycarbonyl)-aminals and  $\beta$ -naphthols as the substrates. 1,2-Addition of  $\beta$ -naphthols to chiral phosphoric acidcatalyzed *in situ* generated *N*-Boc-imines provided chiral propargylamines in moderate to high yields with high to excellent enantioselectivity. Addition of 10 mol% AgOAc and 20 mol% 2,6-lutidine or 1.2 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in the resulting chiral propargylamine solution provided chiral 1,2-dihydronaphtho[2,1-*b*]furans in good yields with high to excellent enantioselectivity and naphtho[2,1-*b*]furans in moderate to high yields, respectively.

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