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tert-Butyldimethylsilyl-Directed Highly Enantioselective Approach to Axially Chiral α-Allenols

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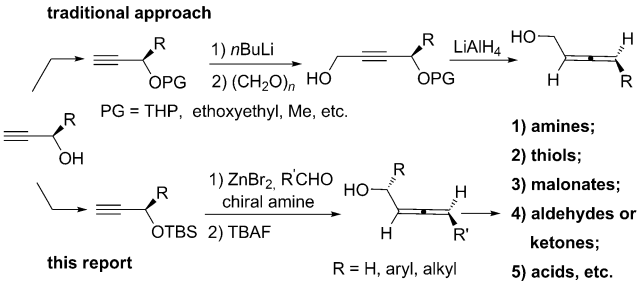
Abstract: A highly efficient and enantioselective synthesis of axially chiral α-allenols was realized in practical yields with 96–99% *ee* or *de* from TBS-protected propargylic alcohols, aldehydes, and a commercially available, inexpensive, chiral, secondary amine (*S*)-α,α-diphenylprolinol or its enantiomer followed by desilylation. The easily removable TBS group not only acts as a protecting group, but also as a possible sterically directing group for the excellent enantioselectivity and in situ prevention of possible allene racemization.

Keywords: allenes · amines · chirality · enantioselectivity · steric hindrance

Introduction

Allenes have become a very important class of basic chemicals in organic synthesis, medicinal chemistry, and materials science;[1] thus, methods for the efficient synthesis of allenes with an axial chirality are currently of high interest.[2] Of particular interest are axially chiral primary α-allenols, which are not only versatile building blocks for the synthesis of different types of heterocycles[3,4] but are also the most basic starting materials for the synthetically attractive axially chiral allenyl amines,[5,6] malonates,[7,8] thiols,[9] aldehydes or ketones,[10] and carboxylic acids.[11] So far, enantioselective synthesis of α-allenols is still challenging due to the fact that such axial chirality spreads over three carbon atoms and there is a free hydroxyl group. Traditionally, a tedious low-yielding route to axially chiral primary α-allenols from optically active propargylic alcohols by using inconvenient and dangerous chemicals such as *n*BuLi and $LiAlH_4$ has been used (Scheme 1).[12] Thus, a highly efficient approach to such primary α-allenols is in great demand. In this paper, we wish to report a straightforward solution to this issue by using TBS, not only as the protecting group, but also as a possible sterically directing group to achieve excellent enantioselectivity. In this approach, the axial chirality is generated highly stereoselectively without racemization, whereas the central chirality, if one is present, remains untouched (Scheme 1).



Scheme 1. Approaches to α-allenols; TBAF = tetrabutylammonium fluoride.

Results and Discussion

Recently, a ZnI_2-mediated one-pot reaction of *p*-nitrobenzyl propargyl ether and *n*BuCHO with (*S*)-α,α-diphenylprolinol [(*S*)-**4**] affording *p*-nitrobenzyl (*R*)-2,3-octadienyl ether in a low yield (46%) with 98% *ee* was realized.[13] However, a number of drawbacks were found for this one-pot reaction: 1) In most cases, the enantioselectivity and yield are not satisfactory or practical with either ZnI_2 or $ZnBr_2$. 2) The results, especially the *ee* values are sometimes time-dependent, thus, not easily reproducible, indicating in situ racemization.[14] 3) Most notably, the reaction of propynol **1a** with CyCHO **2a** afforded only trace amounts of allenol (*R*)-**3aa**, although the starting materials are completely consumed (Table 1, entry 1).[13] After careful analysis of all the failed experimental data for this one-pot transformation, we reasoned that the nature of the substituent on the terminal alkyne should be crucial for obtaining a much more matched reactivity towards aldehydes in the presence of chiral amine **4** as well as improving the enantioselectivity. The

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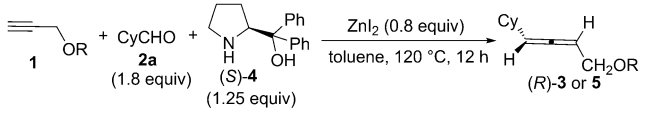
Table 1. Reaction of propynol **1a** and silyl-protected propynols **1b–e**.[a]



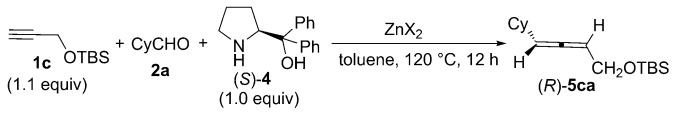
Entry	R	Yield [%][b]	*ee* [%]
1	H (**1a**)	trace [(*R*)-**3aa**]	–[c]
2	TMS (**1b**)	58 [(*R*)-**5ba**]	95[d]
3	TBS (**1c**)	61 [(*R*)-**5ca**]	95[d]
4	TIPS (**1d**)	33 [(*R*)-**5da**]	–[c]
5	TBDPS (**1e**)	34 [(*R*)-**5ea**]	–[c]

[a] The reactions were carried out on a 1.0 mmol scale of **1** in toluene (5 mL). [b] Determined by ^{1}H NMR spectroscopic analysis. [c] Not determined. [d] Determined after desilylation to (*R*)-**3aa**. Cy = cyclohexyl, TMS = trimethylsilyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl, TBDPS = *tert*-butyldiphenylsilyl.

solution would be to identify a sterically bulky, yet easily removable, protecting group (OPG) for propynol. For such a purpose, after many unsuccessful attempts with propargyl carboxylates, a relatively straightforward approach was envisioned that involved steric and shielding effects of silyl groups for the protection of the alcoholic oxygen atom. Gratifyingly, TMS- and TBS-protected propargyl alcohols **1b** and **1c** afforded the axially chiral protected allenols not only in respectable yields (Table 1, entry 1 vs. entries 2 and 3) but also with 95% *ee*. TIPS and TBDPS gave rather lower yields, probably due to their steric bulk (Table 1, entries 4 and 5).

Encouraged by these results and considering the stability, TBS-protected propargyl alcohol **1c** was then chosen for further optimization (Table 2). The enantiomeric purity of (*R*)-**5ca** was improved to 99% when $ZnBr_2$ was used instead of ZnI_2 (Table 2, entry 2);[13] $ZnCl_2$ was less efficient for the reaction (Table 2, entry 3). A preliminary screening on other experimental parameters (Table 2, entries 4–10) led us to define the following optimized conditions (Table 2, entry 10): $ZnBr_2$ (0.75 equiv), (*S*)-**4** (1 equiv), alkyne (1.1 equiv), and aldehyde (1.5 equiv), in toluene at 130°C (10 h), for further study.

Table 2. Optimization of reaction conditions.[a]

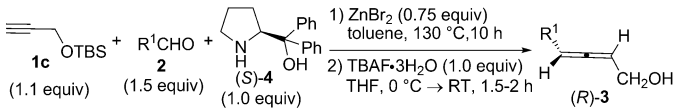


Entry	X ([equiv])	**2a** [equiv]	Yield [%][b]	*ee* [%][c]
1	I (0.8)	1.5	62	95
2	Br (0.8)	1.5	66	99
3	Cl (0.8)	1.5	49	–[d]
4	Br (1.0)	1.5	52	–[d]
5	Br (0.8)	1.3	41	–[d]
6	Br (0.8)	1.7	65	99
7[e]	Br (0.8)	1.5	74	99
8[e]	Br (0.75)	1.5	74	99
9[e]	Br (0.7)	1.5	68	99
10[e,f]	Br (0.75)	1.5	74	99

[a] The reactions were carried out on a 1.0 mmol scale of (*S*)-**4** in toluene (3 mL). [b] Yield determined by ^{1}H NMR spectroscopic analysis. [c] Determined by chiral HPLC after desilylation. [d] Not determined. [e] The reaction was conducted at 130°C. [f] Reaction time: 10 h.

Under the optimized reaction conditions, the scope of the aldehydes is quite general (Table 3); *s*-alkyl (Table 3, entries 1–3, 6, and 9), or *sec*-alkylmethyl (Table 3, entry 4), *n*-alkyl (Table 3, entries 5 and 7), and phenylethyl (Table 3, entry 8) carbinals may all be used, affording the corresponding axially chiral primary α-allenols in decent yields with 96–99% *ee* upon desilylation. When (*R*)-**4** was used as the chiral amine, the enantiomer (*S*)-**3aa** was also conveniently prepared with 99% *ee* (Table 3, entry 3). To demonstrate the practicality of this methodology, the reaction of **1c**, **2a**, or **2b**, and (*S*)-**4** was conducted on a scale of 10 or 3 mmol (Table 3, entries 2 and 3), respectively.

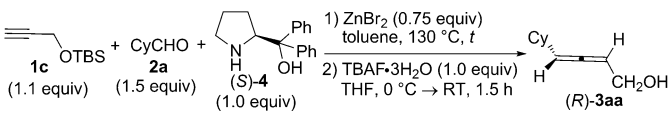
Table 3. Synthesis of axially chiral primary α-allenols.[a]



Entry	R^1	(*R*)-**3** Yield [%][b]	(*R*)-**3** *ee* [%][c]
1	Cy (**2a**)	68 [(*R*)-**3aa**]	99
2[d]	Cy (**2a**)	70 [(*R*)-**3aa**]	99
3[e]	Cy (**2a**)	66 [(*S*)-**3aa**]	99
4[f]	*i*Bu (**2b**)	45 [(*R*)-**3cb**]	98
5	nC_5H_{11} (**2c**)	59 [(*R*)-**3cc**]	98
6	cC_5H_9 (**2d**)	59 [(*R*)-**3cd**]	98
7	nC_7H_{15} (**2e**)	65 [(*R*)-**3ce**]	97
8	$Ph(CH_2)_2$ (**2f**)	60 [(*R*)-**3cf**]	96
9	Et_2CH (**2g**)	63 [(*R*)-**3cg**]	98

[a] The reactions were carried out on a 1.0 mmol scale of (*S*)-**4** in toluene (3 mL) unless otherwise noted. [b] Isolated yields of (*R*)-**3** over two steps. [c] Determined by chiral HPLC analysis. [d] The reaction was conducted on a 10 mmol scale. [e] (*R*)-**4** was used. [f] The reaction was conducted on a 3.0 mmol scale.

It should be noted that racemization of the α-allenol products was not observed, since control experiments showed that (*R*)-**3aa** was consistently obtained with 99% *ee* even when the reaction time was prolonged to 12, 14, or 16 h (Scheme 2).



t/h	*ee*/%
12	99
14	99
16	99

Scheme 2. Synthesis of (*R*)-**3aa** within 12, 14, and 16 h.

Furthermore, this strategy may also be seamlessly applied to the preparation of secondary α-allenols **6fa–ha**, with

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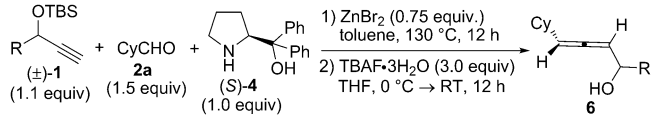
either central or axial chiralities, with high *de* and *ee* values from the corresponding terminal alkynes **1f–h** in practical yields (Table 4). It should be noted that the *ee* and *de* values of **6ha** prepared by this protocol are much higher than those obtained in our previously reported protocol.[13a]

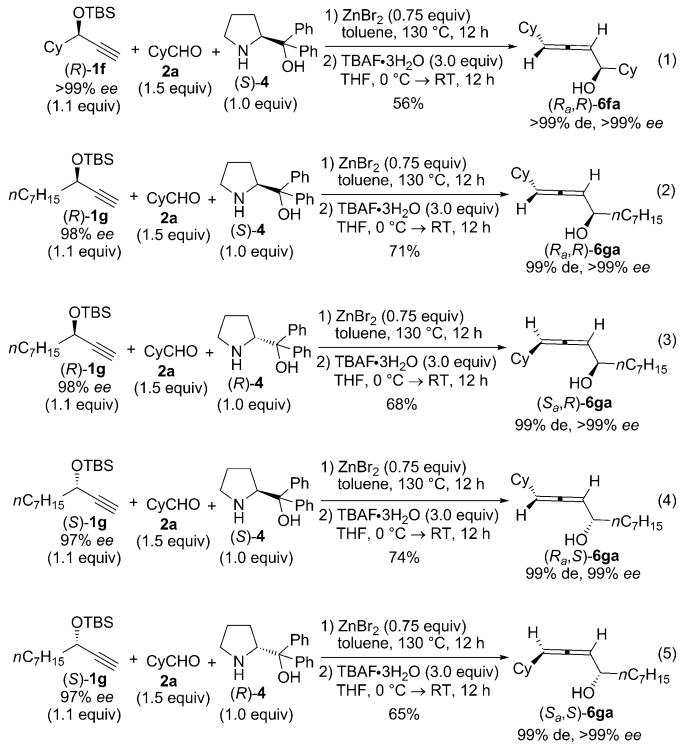
Table 4. Synthesis of axially chiral secondary α-allenols from racemic TBS-protected secondary propargylic alcohols.[a]



R	Isolated yield [%]	(R_a,S)-**6** *de*/*ee* [%][b]	(R_a,R)-**6** *de*/*ee* [%][b]
Cy (**1f**)	61 (**6fa**; *dr* = 1:1.2)	98/99	99/98
nC_7H_{15} (**1g**)	70 (**6ga**; *dr* = 1:1.1)	97/98	98/97
Ph (**1h**)	73 (**6ha**; *dr* = 1.1:1)	99/99	99/99

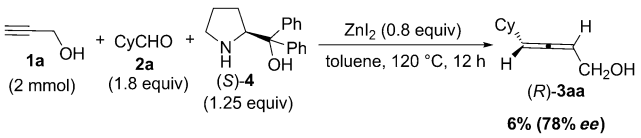
[a] The reactions were carried out on a 1.0 mmol scale of (*S*)-**4** in toluene (3 mL). [b] The *de* values were calculated separately for diastereoisomers having the same central chiralities, that is, (R_a,S) vs. (S_a,S) and (R_a,R) vs. (S_a,R), based on the results shown in Scheme 3.

As expected, the reaction of optically active (*R*)-**1f** afforded allenols (*R*,*R*)-**6fa** in a decent yield and >99% *de*/*ee* [Eq. (1), Scheme 3]. Notably, all of the four diastereoisomers of **6ga** were highly stereoselectively prepared by simply adjusting the absolute configurations of the central chiralities in the TBS-protected secondary propargylic alcohols **1** and α,α-diphenylprolinol **4** [Eqs. (2)–(5), Scheme 3].



Scheme 3. Synthesis of (R_a,R)-**6fa** and four diastereoisomers of **6ga**.

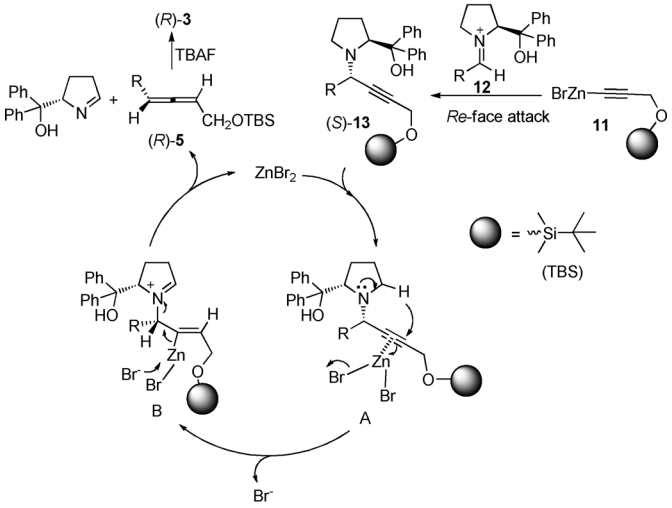
In an effort to shed further light on the role of the TBS group in the protected propargylic alcohols, we scaled up the reaction of the unprotected propynol **1a** with CyCHO **2a** in the presence of (*S*)-α,α-diphenylprolinol **4**. The corresponding allenol (*R*)-**3aa** was obtained in 6% yield (72% purity) with 78% *ee* after careful chromatography on silica gel (Scheme 4), which clearly showed that the TBS group is



Scheme 4. Reaction of unprotected propynol **1a:** the role of TBS.

not merely acting as a protecting group, it is also responsible for the matched reactivity as well as the excellent enantioselectivity for the formation of the optically active propargylic amine intermediate with a central chirality, which is then highly stereoselectively transferred to the axial chirality of the newly generated allene functionality through intramolecular hydride-transfer. In addition, it should be noted here that, under the standard conditions, all the results are easily reproducible, thus, it also helps to prevent the racemization of this in situ generated allene moiety[14] at temperatures as high as 130 °C. The low yielding nature of this primary alcohol may be caused by the strong interaction between Zn^{2+} and the free hydroxyl group, which may cause some side reactions because the alcohol was consumed completely after 12 h.

The absolute configurations of allenes were assigned on the basis of previous studies.[13] A model to predict the absolute configuration of the allene moiety for the highly enantioselective formation of (*R*)-**3** from (*S*)-α,α-diphenylprolinol **4** is shown in Scheme 5.[13,15] The steric bulk of the TBS group in the alkynylzinc specie **11** helps to make an *Re*-face attack of the in situ generated iminium ion **12** more favor-



Scheme 5. Proposed mechanism and prediction of the absolute configuration of the allene.

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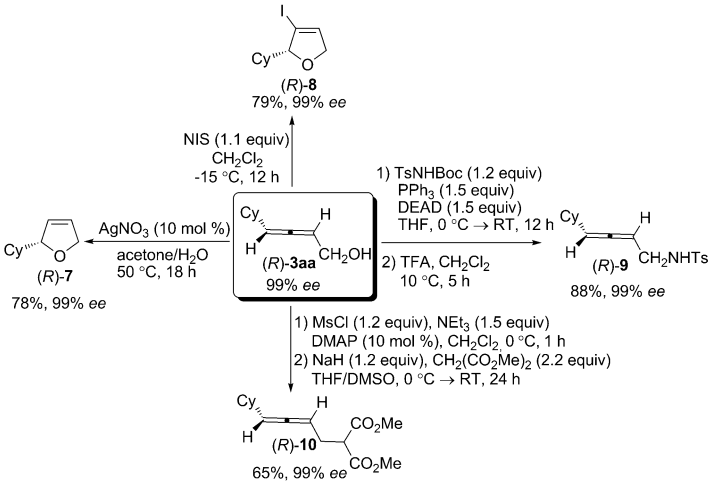
able due to the steric compulsion with the diphenyl moiety in iminium ion **12**, furnishing propargylic amine intermediate (*S*)-**13** highly stereoselectively, which then undergoes intramolecular hydride transfer and β-elimination followed by desilylation to afford (*R*)-**3**. In should be noted that the *p*-nitrobenzyl group in our original report[13a] may also act as a bulky group and therefore lead to excellent enantioselectivity. However, removal of this group is more difficult than that of the TBS group. It should also be noted that the size of the protecting group is crucial for this transformation: very bulky groups such as TIPS or TBDPS gave lower yields, as shown in Table 1.

These enantioenriched primary α-allenols are very useful precursors of a variety of synthetically useful, but not readily available, optically active heterocyclic compounds with a central chirality, or functionalized allenes with an axial chirality (Scheme 6). For example, silver-catalyzed cycloisomerization[3e,16] and iodocyclization with NIS (NIS = *N*-iodosuccinimide)[17] afforded dihydrofuran (*R*)-**7** and (*R*)-**8** with complete transfer of the axial chirality; optically active allenyl amine (*R*)-**9**[6] or (2,3-butadienyl)malonate (*R*)-**10**[8] may also be prepared with 99% *ee* by the Mitsunobu reaction[18] followed by deprotection or nucleophilic substitution, respectively.



Scheme 6. Transformations of axially chiral α-allenol (*R*)-**3aa**; Ts = tosyl, Boc = *tert*-butoxycarbonyl, DEAD = diethyl azodicarboxylate, TFA = trifluoroacteic acid, Ms = methane sulfonyl, DMAP = 4-dimethylaminopyridine.

Conclusion

We have developed a straightforward route to axially chiral α-allenols from TBS-protected propargylic alcohols, aldehydes, and inexpensive, commercially available (*R*)- or (*S*)-α,α-diphenylprolinol **4** in practical yields with very high efficiency for the generation of the axial chirality due to the introduction of the sterically bulky, yet easily attachable and removable, nature of the TBS group. Because of the ready availability of the starting materials, the simplicity of the manipulation, as well as the potentials of the axially chiral α-allenols, this methodology will be of high importance to the scientific community. Further studies on the scope, working mechanism for the effect of TBS, and synthetic applications are being pursued in our laboratory.

Experimental Section

Synthesis of (*R*)-4-cyclohexyl-2,3-butadien-1-ol (*R*-3aa); Typical procedure: To a 100 mL flame-dried, three-necked flask was added $ZnBr_2$ (1.6912 g, 7.5 mmol). The flask was dried under vacuum with a heating gun. Compound (*S*)-**4** (2.5857 g, 10 mmol, 98%), **1c** (1.8738 g, 11 mmol) in toluene (20 mL), and **2a** (1.6831 g, 15 mmol) in toluene (10 mL) were then added sequentially under an Ar atmosphere. The flask was then equipped with a condenser and placed in a pre-heated oil bath at 130 °C, with stirring. After 10 h, the reaction was complete as monitored by TLC. After cooling to RT, the crude reaction mixture was filtered through a short pad of silica gel and eluted with ether (50 mL). After evaporation, the residue was filtered through a short column of silica gel (petroleum ether/ethyl ether = 50:1) to collect the nonpolar TBS-protected allenol after evaporation. The allenol was directly dissolved in THF (30 mL) without further characterization and treated at 0 °C with TBAF·3H_2O (3.1563 g, 10 mmol). The resulting mixture was allowed to warm to RT with stirring. After 1.5 h, the reaction was complete (reaction monitored by TLC analysis), and H_2O (20 mL) and ether (20 mL) were then added. The organic layer was separated and the aqueous layer was extracted with ether (3 × 20 mL). The combined organic layer was washed with brine (20 mL) and dried over anhydrous Na_2SO_4. After filtration and evaporation, the residue was purified with chromatography on silica gel (petroleum ether/ethyl acetate = 15:1→10:1) to afford (*R*)-**3aa** (1.0624 g, 70%) as a liquid: 99% *ee* [HPLC conditions: Chiralcel AS-H column; hexane/*i*PrOH = 98:2; 0.6 mL min^{-1}; λ = 214 nm; t_R = 11.9 (major), 12.9 min (minor)]; $[\alpha]_D^{22} = -100.3$ (c = 1.00, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, 25 °C, TMS): δ = 5.42–5.26 (m, 2H; CH=C=CH), 4.11 (s, 2H; OCH_2), 2.07–1.94 (m, 1H; CH from Cy), 1.82–1.49 (m, 6H; OH and protons from Cy), 1.36–1.00 ppm (m, 5H; protons from Cy); ^{13}C NMR (75 MHz, $CDCl_3$, 25 °C, TMS): δ = 201.8, 99.7, 92.5, 60.7, 36.9, 33.0, 32.9, 26.0, 25.9 ppm; IR (neat): $\tilde{\nu}$ = 3326, 2923, 2850, 1961, 1448, 1302, 1259, 1214, 1062, 1008 cm^{-1}; MS (70 eV): m/z (%): 152 (0.70) $[M]^+$, 55 (100); HRMS: m/z calcd for $C_{10}H_{16}O$: 152.1201 [M^+]; found: 152.1203.

Acknowledgements

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