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Highly Enantioselective Synthesis Using Prolinol as a Chiral Auxiliary: Silver-Mediated Synthesis of Axially Chiral Vinylallenes and Subsequent (Hetero)-Diels−Alder Reactions

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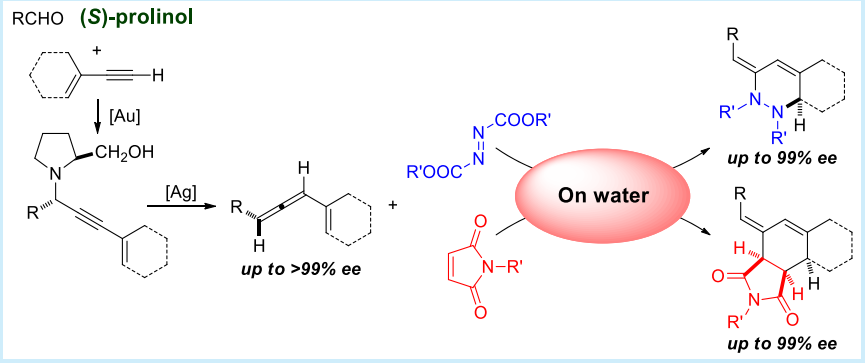
Supporting Information



ABSTRACT: Using (*S*)-prolinol as a chiral auxiliary, axially chiral vinylallenes with excellent enantiopurity (up to >99% enantiomeric excess (ee)) were readily prepared from optically pure propargylamines in the presence of $AgNO_3$ under microwave irradiation. Subsequent (hetero)-Diels−Alder reaction of these axially chiral vinylallenes with azodicarboxylates or maleimides on water demonstrates excellent axial-to-point chirality transfer (up to 99% ee).

The pursuit of highly efficient and enantioselective reactions for the construction of complex molecules with point/axial chirality is everlasting in synthetic organic chemistry.[1] In the context of cost and time effectiveness, the development of highly enantioselective reactions using inexpensive metal reagents and readily available chiral auxiliaries is beneficial for asymmetric synthesis of organic molecules featuring diverse and complex structures with practical applications.

Axially chiral allenes are important structural motifs present in natural products[2] and are versatile chiral synthons attributed to axial-to-point chirality transfer.[3] In particular, vinylallenes are flexible building blocks, because they can undergo various cycloaddition reactions.[4] However, the few preparation methods for this class of compounds[4e−g,5] may limit the advancement of their chemistry. Previously, we reported an efficient protocol for easy access of axially chiral allenes from optically pure propargylamines mediated by $AgNO_3$ using (*S*)-prolinol as a chiral auxiliary under microwave irradiation.[6] Extension of this protocol to the synthesis of vinylallenes was found to be successful.

In our endeavor to develop silver-catalyzed highly enantioselective organic transformation reactions,[7] we describe the silver(I)-mediated highly enantioselective synthesis of axially chiral vinylallenes (up to 94% yield with >99% enantiomeric excess (ee)), using (*S*)-prolinol as the chiral auxiliary, and their subsequent (hetero)-Diels−Alder reaction with azodicarboxylates or maleimides on water to give the corresponding cycloadducts in good to excellent yields (43%−98%) with excellent axial-to-point chirality transfer (up to >99% ee) under mild conditions.

Axially chiral vinylallenes, including those new in this work, were prepared from optically active propargylamines in the presence of 0.5 equiv of $AgNO_3$.[6] The results are summarized in Table 1. Under microwave irradiation (50 W) for 20 min at 70 °C, axially chiral vinylallenes **1a**−**1i** bearing electron-donating or withdrawing aryl substituents were synthesized in 56%−94% isolated yields based on 52%−100% substrate conversions with good to excellent enantioselectivity (between 79% ee and >99% ee), using (*S*)-prolinol as a chiral auxiliary. The synthesis of **1j**, bearing an *iso*-propenyl group required a longer reaction time (1 h) for significant substrate conversion (82%). Vinylallene **1a′**, the enantiomer of **1a**, was prepared using (*R*)-prolinol as a chiral auxiliary in good yield (67%

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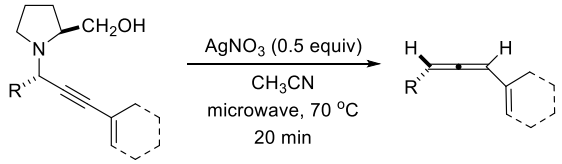
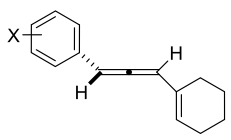
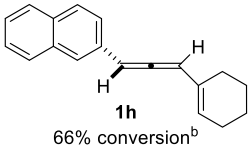
Table 1. $AgNO_3$-Mediated Preparation of Axially Chiral Vinylallenes from Optically Active Propargylamines with (*S*)-Prolinol as a Chiral Auxiliary[a]

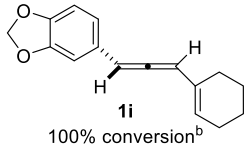




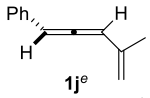
			conversion[b]	yield[c]	ee[d]
X =	*p*-H	**1a**	100%	78%	98%
	p-Cl	**1b**	71%	91%	96%
	p-F	**1c**	74%	94%	98%
	p-Me	**1d**	100%	80%	96%
	p-OMe	**1e**	100%	75%	82%
	p-COOMe	**1f**	100%	56%	>99%
	m-CHO	**1g**	52%	87%	98%



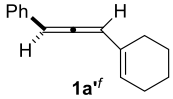
1h
66% conversion[b]
89% yield[c]
98% ee[d]



1i
100% conversion[b]
80% yield[c]
79% ee[d]



1j[e]
82% conversion[b]
83% yield[c]
98% ee[d]



1a'[f]
100% conversion[b]
67% yield[c]
99% ee[d]

[a]Reaction conditions: propargylamines (0.4 mmol), $AgNO_3$ (0.2 mmol, 0.5 equiv), CH_3CN (4 mL), microwave (50 W) at 70 °C for 20 min. [b]Determined by ^1H NMR analysis of the crude reaction mixture. [c]Isolated yield based on conversion of propargylamine. [d]Determined by HPLC, using a Chiralcel OD-3 column. [e]Reaction time = 1 h. [f](*R*)-Prolinol as a chiral auxiliary.

isolated yield based on 100% substrate conversion) with comparable enantiopurity (99% ee). These findings further support that the protocol allows for easy and efficient access to axially chiral vinylallenes with high enantiopurity, and prolinol serves as an inexpensive and efficient chiral auxiliary for point chirality induction in propargylamines, which is, in turn, transferred to the axial chirality in vinylallenes.

The enantiomeric excess (ee) values of the vinylallenes was found to be dependent to the electronic property of the substituents on the aryl ring; ee was higher for vinylallenes bearing electron-withdrawing groups such as −F (98% ee) or −COOMe (>99% ee), and the opposite was observed with electron-donating groups such as −Me (95% ee) or −OMe (82% ee). This trend was also observed for gold-catalyzed preparation of axially chiral allenes,[6,8] and is presumably due to subsequent racemization via the coordination of the metal ion to the allene moiety.[9]

Further reaction of these axially chiral vinylallenes was then explored. Hetero-Diels−Alder reactions of the vinylallene with azodicarboxylates was selected as the first reactions to try, since reports on such transformations are scarce.[10] Under the optimized condition (see Table S1 in the Supporting Information for the optimization details), 0.10 mmol of **1a** (98% ee in *R* configuration, 1 equiv) reacted with 0.11 mmol of diethyl azodicarboxylate (DEAD; 1.1 equiv) in 1 mL of H_2O at room temperature (rt) for 0.5 h, giving cycloadduct **2a** as a single product in 96% isolated yield based on 97% conversion of **1a** with 98% ee (entry 1 in Table 2). Cycloadduct **2a′** (the enantiomer of **2a**) was obtained using **1a′** as the substrate with comparable substrate conversion, isolated yield, and ee, as were observed in the synthesis of **2a** (entry 2 in Table 2).

This reaction showed high functional group tolerance (Table 2). Vinylallenes bearing halogens (**1b** and **1c**; entries 3 and 4 in Table 2), Me (**1d**; entry 5 in Table 2), OMe (**1e**; entry 6 in Table 2), COOMe (**1f**; entry 7 in Table 2), CHO (**1g**; entry 8 in Table 2), naphthalene (**1h**; entry 9 in Table 2) and 1,3-benzodioxole (**1i**; entry 10 in Table 2) groups underwent the reaction with DEAD on water at rt to give the corresponding cycloadducts in good to excellent yields (76%−98% yield, based on 67%−98% substrate conversion) with excellent axial-to-point chirality transfer within 0.5 h. The effect of the alkyl group on the azodicarboxylate was also examined (Table 2). While changing the −Et group of the azodicarboxylate to −^{i}Pr did not exert significant steric hindrance to the cycloaddition reaction, leading to **2k** in 83% yield, based on complete substrate conversion with 98% ee (entry 12, Table 2), the presence of a −^{t}Bu group led to a reduction in both substrate conversion and isolated yield (66% isolated yield, based on 85% conversion with 98% ee; entry 13 in Table 2). **1a** could also underwent cycloaddition with 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) smoothly to give **2m** in 91% yield with 97% ee (see Scheme 1).

The absolute configuration of **2a** was determined by X-ray crystallographic analysis. Crystal of **2a** suitable for X-ray crystallographic analysis was obtained by slow evaporation of solvent from a solution of **2a** in 10% isopropyl alcohol in hexane at rt. As shown in Figure 1, the newly formed chiral center (C1 in Figure 1) is determined as in *R* configuration, supportive to the convention Diels−Alder reaction mechanism that the azodicarboxylate approaches from the opposite side of the aryl group of the vinylallene, which is less hindered.

The Diels−Alder reactions of vinylallenes with maleimides was also studied (see Table 3). Compared to the reaction with azodicarboxylates, the reactions with maleimides require a higher reaction temperature (40 °C) and a longer reaction time (4 h; see Table S2 in the Supporting Information for the optimization details). Under the optimized condition, 0.10 mmol of vinylallene **1a** (98% ee in *R* configuration, 1 equiv) reacted with 0.11 mmol of *N*-methylmaleimide (1.1 equiv) in 1 mL of H_2O at 40 °C for 4 h, giving cycloadduct **3a** in 69% isolated yield, based on 93% conversion with an *endo*:*exo* ratio of 92:8 and 98% ee for the major diastereomer (entry 1 in Table 3). The relative configuration of the three fused rings of **3a** was determined by nuclear Overhauser effect spectroscopy (NOESY) (see the Supporting Information).

Vinylallenes **1b**−**1i** bearing various electron-donating or electron-withdrawing substituents underwent cyclization with *N*-methylmaleimide smoothly to form the corresponding cycloadducts **3b**−**3i** in moderate to excellent yields (48%−98%) with >90:10 *endo*:*exo* ratio and excellent axial-to-point chirality transfer (entries 2−9 in Table 3). Vinylallene **1j** bearing *iso*-propenyl group also underwent the cycloaddition reaction to give **3j** in 69% isolated yield, based on 95% substrate conversion with 96% ee (entry 10 in Table 3). It is observed that the Diels−Alder reactions involving vinylallenes **1f** and **1h** bearing COOMe and naphthalene, respectively, proceeded with low substrate conversion (26% for **1f**, 35% for

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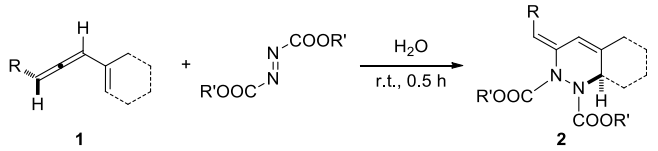
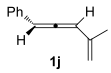
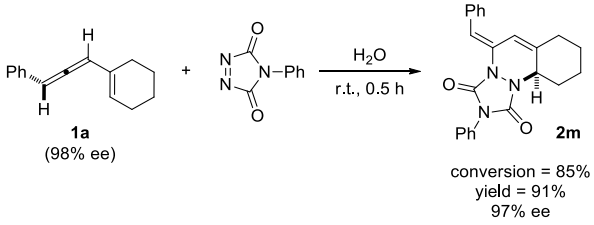
Table 2. Substrate Scope of Hetero-Diels–Alder Reactions of 1 with Azodicarboxylates[a]



entry	R		R'	compd	conversion[b]/%	yield[c]/%	ee[d]/%
1	Ph (98% ee)	**1a**	Et	**2a**	97	96	98
2	**1a'** (99% ee)		Et	**2a'**	97	97	99
3	*p*-Cl(C_6H_4) (96% ee)	**1b**	Et	**2b**	97	81	96
4	*p*-F(C_6H_4) (98% ee)	**1c**	Et	**2c**	97	93	98
5	*p*-Me(C_6H_4) (96% ee)	**1d**	Et	**2d**	98	88	96
6	*p*-OMe(C_6H_4) (82% ee)	**1e**	Et	**2e**	83	88	82
7	*p*-COOMe(C_6H_4) (>99% ee)	**1f**	Et	**2f**	77	95	99
8	*m*-CHO(C_6H_4) (98% ee)	**1g**	Et	**2g**	97	98	98
9	 (98% ee)	**1h**	Et	**2h**	67	91	97
10	 (79% ee)	**1i**	Et	**2i**	90	76	80
11	 **1j** (97% ee)		Et	**2j**	68	77	--[e]
12	**1a** (98% ee)		^{i}Pr	**2k**	100	83	98
13	**1a** (98% ee)		^{t}Bu	**2l**	85	66	98

[a]Reaction conditions: **1** (0.10 mmol), azodicarboxylate (0.11 mmol), H_2O (1 mL). [b]Determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Isolated yield based on conversion of **1**. [d]Determined by HPLC using a Chiralcel AD-3 or AD-H column. [e]**2j** does not contain any chiral C center.

Scheme 1. Reaction of 1a with PTAD



1h; entries 6 and 8 in Table 3). These results are likely due to the fact that both of these vinylallenes and *N*-methylmaleimide are all insoluble solids in water at rt.

Changing the dienophile to *N*-phenylmaleimide afforded **3k** in 80% isolated yield, based on 95% conversion, with excellent *endo*:*exo* ratio (96:4) and ee (98%; entry 11 in Table 3). Maleimide, with free N–H moiety, also underwent Diels–Alder reaction with **1a**, giving **3l** in 43% isolated yield, based

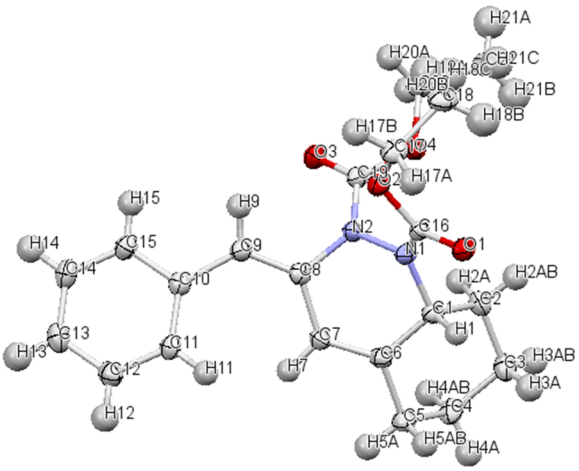


Figure 1. ORTEP drawing of **2a**. Non-hydrogen atoms are represented by thermal ellipsoids drawn at the 30% probability level.

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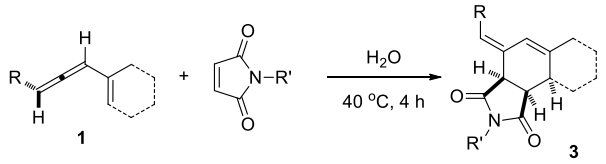
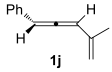
Table 3. Substrate Scope of Diels–Alder Reactions of 1 with Maleimides[a]



entry	R		R'	compd	conversion[b]/%	yield[c]/%	*endo*:*exo*[b]	ee[d]/%
1	Ph (98% ee)	**1a**	Me	**3a**	93	69	92:8	98
2	*p*-Cl(C_6H_4) (96% ee)	**1b**	Me	**3b**	77	54	95:5	96
3	*p*-F(C_6H_4) (98% ee)	**1c**	Me	**3c**	89	59	94:6	98
4	*p*-Me(C_6H_4) (96% ee)	**1d**	Me	**3d**	77	74	92:8	96
5	*p*-OMe(C_6H_4) (82% ee)	**1e**	Me	**3e**	90	77	96:4	82
6	*p*-COOMe(C_6H_4) (>99% ee)	**1f**	Me	**3f**	26	98	>99:1	>99
7	*m*-CHO(C_6H_4) (98% ee)	**1g**	Me	**3g**	92	68	96:4	98
8	 (98% ee)	**1h**	Me	**3h**	35	48	94:6	95
9	 (79% ee)	**1i**	Me	**3i**	91	67	93:7	79
10	 **1j** (97% ee)		Me	**3j**	95	69	--[e]	96
11	**1a** (98% ee)		Ph	**3k**	95	80	96:4	98
12	**1a** (98% ee)		H	**3l**	53	43	89:11	98

[a]Reaction conditions: **1** (0.10 mmol), maleimide (0.11 mmol), H_2O (1 mL). [b]Determined by ^1H NMR analysis of the crude reaction mixture. [c]Isolated yield based on conversion of **1**. [d]Determined by HPLC using a Chiralcel AD-H column. [e]Only a single diastereomer was obtained for **3j**.

on 53% substrate conversion and with 89:11 *endo*:*exo* ratio and 98% ee (entry 12 in Table 3).

To conclude, axially chiral vinylallenes with excellent enantiopurity (up to >99%) can be efficiently prepared from propargylamines mediated by $AgNO_3$, using (*S*)-prolinol as a chiral auxiliary. These axially chiral vinylallenes can undergo highly enantioselective (hetero)-Diels–Alder reaction, leading to cycloadducts in good to excellent yields (up to 98%) with excellent axial-to-point chirality transfer (up to 99% ee).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b02514.

Detailed experimental procedure, spectral data (PDF)

Accession Codes

CCDC 1937998 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_ request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

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Author Contributions

The manuscript was written through contributions of all authors.

Notes

The authors declare no competing financial interest.

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