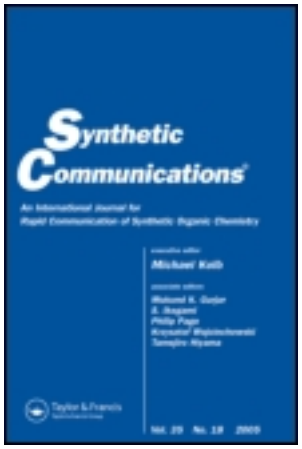

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STEREOSELECTIVE SYNTHESIS OF 1,3-DIENES FROM PROPARGYLIC ALCOHOLS BY $LiAlH_4/AlCl_3$

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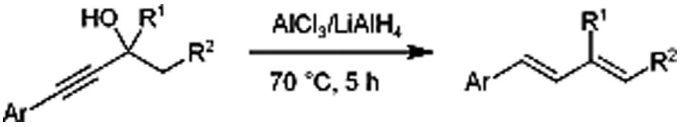
GRAPHICAL ABSTRACT



Abstract *Herein we report that $LiAlH_4/AlCl_3$ is a very efficient reagent for the reductive dehydration of aryl propargylic alcohols in tetrahydrofuran solvent at reflux to give 1,3-dienes with good yields and high* E *selection. The reaction conditions are mild and easy to operate, and a variety of aryl functional groups, such as bromo, fluoro, butyl, and methoxyl groups, are tolerated. With our protocol, useful (*E,E*)-1,3-dienes can be synthesized.*

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Keywords Dehydration; 1,3-diene; propargylic alcohol; reduction; stereoselection

INTRODUCTION

Olefin metathesis is an important method for C-C double bond formation in organic synthesis.[1] In particular, the Diels–Alder reaction of 1,3-dienes has been utilized to construct a diverse set of organic molecules.[2] A wide variety of methods exists for the construction of stereodefined 1,3-dienes. These include Wittig,[3] Julia–Kocienski,[4] Suzuki cross coupling,[5] and other reactions.[6] Despite their advantages, several drawbacks remain associated with such reactions, including poor stereoselectivity, the generation of by-products, and the use of stereodefined coupling partners and expensive transition-metal catalysts. Thus, the development of new methods for their stereoselective synthesis is still needed.

On the other hand, lithium aluminum hydride ($LiAlH_4$) is used for the reduction of various functionalities and also acts as a highly selective reducing agent for pro-

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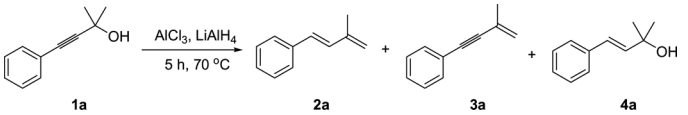
pargylic alcohols.[7] We have envisaged that $LiAlH_4$-catalyzed *E*-selective reduction of propargylic alcohols followed by Lewis acid–catalyzed dehydration could be a valuable and complementary synthetic method for one-pot conversion of propargylic alcohols into conjugated (*E*)-dienes.[8] Therefore, in this article, we report a facile one-pot preparation of (*E*)-dienes from propargylic alcohols by $LiAlH_4/AlCl_3$.

RESULTS AND DISCUSSION

Our studies began with the use of acetone-derived 2-methyl-4-phenylbut-3-yn-2-ol (**1a**) as the substrate for reductive/dehydrative reaction. The reaction mixture consisting of **1a**, $LiAlH_4$ (2 equiv), and $AlCl_3$ (3 equiv) was heated to reflux in tetrahydrofuran (THF) to produce exclusively (*E*)-1-(3-methylbuta-1,3-dienyl)benzene (**2a**) at 79% isolated yield (Table 1, entry 1). Formation of **2a** was closely related with the amount of $LiAlH_4$ and $AlCl_3$ used in the reaction: When **1a** was treated with 2 equiv of $LiAlH_4$ to yield **2a** and dehydrative product **3a** at a 65:35 mixture, $AlCl_3$ was reduced to 1 equiv, and the yield of diene derivative **2a** became considerably lower (entries 3 and 6). Importantly, only dehydrative product **3a** or reductive product **4a** was obtained in the absence of $LiAlH_4$ or $AlCl_3$ (entries 4 and 7). Different solvents were screened, and THF was found to be the best one (entries 8 and 9). Other Lewis acids such as $ZnCl_2$, $InCl_3$, and $FeCl_3$ failed to give the corresponding diene. The C-C double bond configuration was confirmed by the coupling constant of the protons in ^1H NMR studies.

Given our optimized conditions, we investigated the scope of this one-pot reaction sequence using various aryl- and furan-substituted propargylic alcohols (Table 2). Therefore, both electron-rich and electron-deficient aryl-substituted tertiary propargylic alcohols were evaluated, yielding the corresponding 1,3-dienes in good to excellent yields with high *E* selectivity (Table 2, entries 1–5). The

Table 1. Reductive dehydration of propargylic alcohol **1a** by $LiAlH_4/AlCl_3$[a]



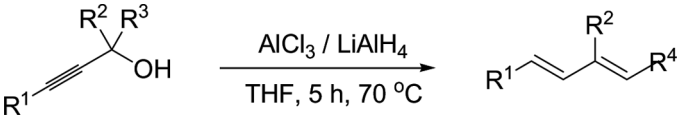
1a **2a** **3a** **4a**

Entry	$AlCl_3$ (eq.)	$LiAlH_4$ (eq.)	Solvent	Yield (%) of (**2a**/**3a**/**4a**)[b]
1	2	3	THF	79 (100/0/0)
2	2	4	THF	35 (100/0/0)
3	2	2	THF	82 (65/35/0)
4	1	0	THF	87 (0/100/0)
5	3	3	THF	76 (100/0/0)
6	1	3	THF	58 (100/0/0)
7	0	3	THF	50 (0/0/100)
8	2	3	ether	71 (48/52/0)
9	2	3	$(CH_2Cl)_2$	trace
10	2	3	dioxane	trace

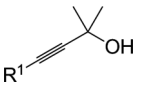
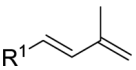
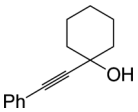
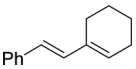
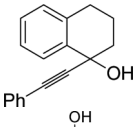
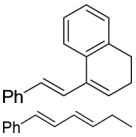
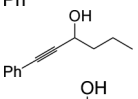
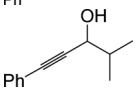
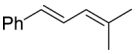
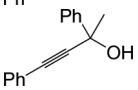
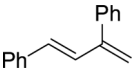
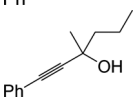
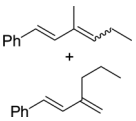
[a]The reactions were performed with **1a** (1 mmol), $AlCl_3$ (0–3 mmol), and $LiAlH_4$ (0–4 mmol) in solvent (2 mL) at 70 °C for 5 h.

[b]Isolated yields. The ratios of **2a**, **3a**, and **4a** were determined by GC.

Table 2. Reaction scope for one-pot synthesis of (*E*)-dienes from propargylic alcohols[a]



1 **2**

Entry	Acetylenic alcohol	1	Diene	2	Yield (%)[b]
1		**1b**: R^1 = 4-BrPh		**2b**	75
2		**1c**: R^1 = 3-FPh		**2c**	90
3		**1d**: R^1 = 4-n-BuPh		**2d**	65
4		**1e**: R^1 = 4-MeOPh		**2e**	92
5		**1f**: R^1 = 3,4-MeOPh		**2f**	87
6		**1g**: R^1 = 3-futanyl		**2g**	67
7		**1h**: R^1 = *E*-PhCH=CH		**2h**	88
8		**1i**		**2i**	79
9		**1j**		**2j**	85
10		**1k**		**2k**	75
11		**1l**		**2l**	65
12[c]		**1m**		**2m**	95
13		**1n**		**2n1** + **2n2**	71 (1:1)[d]

[a]The reactions were performed with 1.0 mmol of **1a**, 2 mmol of $AlCl_3$, and 3 mmol of $LiAlH_4$ in 2 mL of THF at 70 °C for 5 h.

[b]Isolated yields.

[c]The reactions were performed with 1.0 mmol of **1a** and 3 mmol of $LiAlH_4$ in 2 mL of THF at 70 °C for 5 h and then with $AlCl_3$ (2 mmol) at 70 °C for 3 h.

[d]The ratio of **2n1** and **2n2** was determined by ^{1}H NMR.

furan-substituted propargylic alcohol **1g** was also a suitable reaction partner (Table 2, entry 6). When acetone and (*E*)-1-(but-1-en-3-ynyl)benzene-derived propargylic alcohol **1h** was used as the substrate, the desired (*E,E,E*)-triene **2h** was obtained stereoselectively (Table 2, entry 4). Even bulky cyclohexanone- and tetralone-derived tertiary propargylic alcohols **1i** and **1j** gave good product yields, and acetophenone-derived propargylic

alcohol **1m** provided a good yield of product (Table 2, entries 8, 9, and 12). Furthermore, aldehyde-derived secondary aryl propargylic alcohol tended to give (*E,E*)-1,3-diene **2k** with high stereoselectivity, and the sterically hindered propargylic alcohol **1l** was also tolerated (Table 2, entries 10 and 11). With different alkyl groups (R^2, R^3) occupied on the aryl propargylic alcohol **1n**, the reaction proceeded smoothly, giving **2n1** and **2n2** as a 50:50 mixture (Table 2, entry 13).

In summary, the present study illustrates the feasibility and broad applicability of $LiAlH_4/AlCl_3$-catalyzed reduction/dehydration of aryl propargylic alcohols. Moreover, reaction setup and execution of the two-step, one-pot sequence are simple, and the method provides the target 1,3-dienes in excellent yields with good stereoselectivity. Additionally, this transformation tolerates a wide range of functional groups on the aryl-substituted part, and a series of secondary or tertiary propargylic alcohols could be applied.

EXPERMENTAL

General Procedure for Dienes 2a–2n

To a mixture of $LiAlH_4$ (3 mmol), and $AlCl_3$ (2 mmol) in anhydrous THF (4 mL) was added propargylic alcohol (1 mmol). The mixture was then stirred at 70 °C until the starting propargylic alcohol was consumed as judged by thin-layer chromatography. The mixture was quenched with saturated solution of NH_4Cl and then extracted with ethyl acetate (20 mL × 3). The organic layer was washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by column chromatography (silica gel) to yield product in an analytically pure form.

(*E*)-1-Fluoro-3-(3-methylbutA-1, 3-dien-1-yl)benzene (2c)

Pale yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29–7.24 (m, 1H), 7.18–7.16 (m, 1H), 7.14–7.11 (m, 1H), 6.93–6.89 (m, 1H), 6.87 (d, $J = 16.0$ Hz, 1H), 6.48 (d, $J = 16.0$ Hz, 1H), 5.14 (s, 1H), 5.11 (s, 1H), 1.96 (s, 3H).^{13}C NMR (125 MHz, $CDCl_3$): δ 163.2 (d, $J = 242.5$ Hz), 141.7, 139.8 (d, $J = 8.8$ Hz), 133.0, 130.0 (d, $J = 8.8$ Hz), 127.5 (d, $J = 1.2$ Hz), 122.4, 118.3, 114.2 (d, $J = 22.5$ Hz), 112.7 (d, $J = 21.3$ Hz), 18.5. IR (KBr, cm^{-1}): 3417, 2994, 1761, 1756, 1636, 1384, 1246, 1051. HRMS (EI) ($[M]^+$) calcd. for $C_{11}H_{11}F$: 162.0845; found 162.0842.

Complete experimental details are available online in the Supporting Information.

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