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Subtle Electronic Effects in Metal-Free Rearrangement of Allenic Alcohols

Venkata R. Sabbasani,[†] Phani Mamidipalli,[†] Huijie Lu,[‡] Yuanzhi Xia,[‡] and Daesung Lee*,[†]

Department of Chemistry, University of Illinois at Chicago, 845 West Taylor Street, Chicago, Illinois 60607, United States, and College of Chemistry and Materials Engineering, Wenzhou University, Wenzhou, Zhejiang Province 325035, P. R. China

dsunglee@uic.edu

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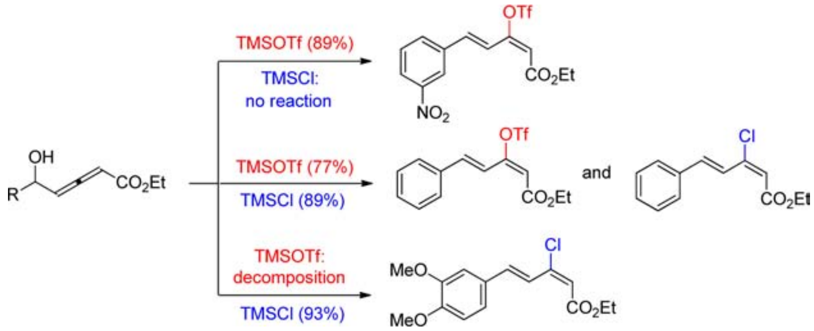
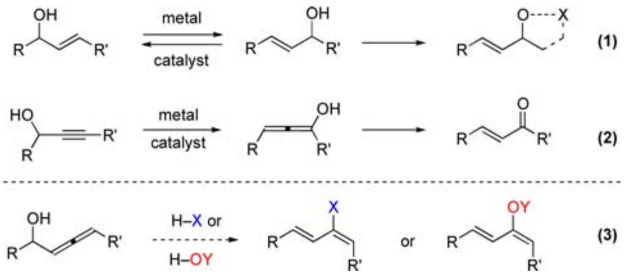
ABSTRACT



A general and stereoselective rearrangement of allenic alcohols to (*E,E*)-1,3-dien-2-yl triflates and chlorides was developed under metal-free conditions. Subtle electronic effects of the alkyl and aryl substituents on the carbon bearing the hydroxyl group has a profound impact on the reaction rate and efficiency such that vinyl triflates were obtained from electron-deficient substrates and trimethylsilyl triflate whereas vinyl chlorides were generated with an electron-rich substrate and trimethylsilyl chloride.

Scheme 1



Allylic 1,3-transposition of C–O bonds across a π-system is an important transformation in organic synthesis. The 1,3-transposition of allylic[1] and propargylic[2] alcohols and their acyl derivatives has been extensively studied under oxo-metal or Lewis acid catalyzed conditions (Scheme 1, eqs 1 and 2). On the other hand, the corresponding rearrangement of allenic alcohols or their derivatives (eq 3) has been virtually ignored until recently except for a few examples. Trost realized aldol reactions between aldehydes and enolates derived from allenic alcohols via 1,3-transposition in the

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[†] University of Illinois at Chicago.

[‡] Wenzhou University.

(1) (a) Takai, K.; Nozaki, H.; Oshima, K.; Okazoe, T.; Matsubara, S. *Bull. Chem. Soc. Jpn.* **1985**, *58*, 844–849. (b) Narasaka, K.; Kusama, H.; Hayashi, Y. *Tetrahedron* **1992**, *48*, 2059–2068. (c) Gordon, M. S.; Jensen, J. H.; Espenson, J. H.; Jacob, J. *Organometallics* **1998**, *17*, 1835–1840. (d) Wang, G.; Jimtaisong, A.; Luck, R. L. *Organometallics* **1998**, *17*, 4522–4525. (e) Le Ny, J.-P.; Bellemin-Laponnaz, S. C. R. *Chimie* **2002**, *5*, 217–224. (f) Morrill, C.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 2842–2843. Related examples with vinyl oxiranes: (g) Batory, L. A.; McInnis, C. E.; Njardarson, J. T. *J. Am. Chem. Soc.* **2006**, *128*, 16054–16055. (h) Herrmann, A. T.; Saito, T.; Stivala, C. E.; Tom, J.; Zakarian, A. *J. Am. Chem. Soc.* **2010**, *132*, 5962–5963. (i) Mustard, T. J.; Mack, D. J.; Njardarson, J. T.; Cheong, P. H.-Y. *J. Am. Chem. Soc.* **2013**, *135*, 1471–1475.

(2) (a) Georgy, M.; Boucard, V.; Campagne, J.-M. *J. Am. Chem. Soc.* **2005**, *127*, 14180–14181. (b) Engel, D.; Dudley, G. B. *Org. Lett.* **2006**, *8*, 4027–4029. (c) Yu, M.; Li, G.; Wang, S.; Zhang, L. *Adv. Synth. Catal.* **2007**, *349*, 871–875. (d) Ramón, R. S.; Marion, N.; Nolan, S. P. *Tetrahedron* **2009**, *65*, 1767–1773. (e) Ye, L.; Zhang, L. *Org. Lett.* **2009**, *11*, 3646–3649. (f) Gaillard, S.; Bosson, J.; Ramn, R. S.; Nun, P.; Slawin, A. M. Z.; Nolan, P. S. *Chem.—Eur. J.* **2010**, *16*, 13729–13740. (g) Pennell, M. N.; Unthank, M. G.; Turner, P.; Sheppard, T. D. *J. Org. Chem.* **2011**, *76*, 1479–1482.

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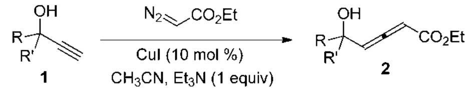
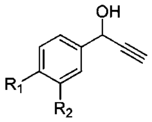
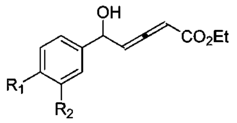
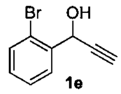
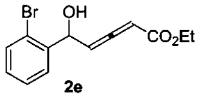
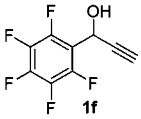
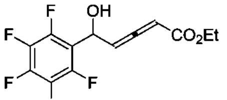
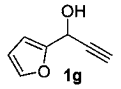
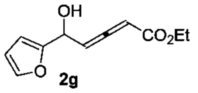
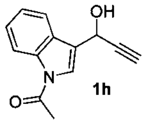
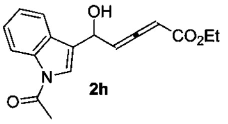
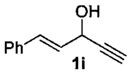
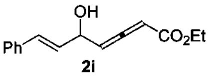
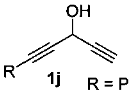
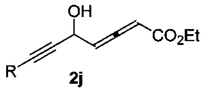
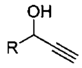
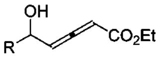
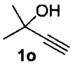
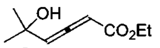
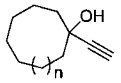
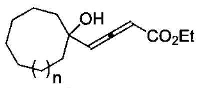
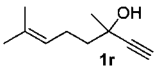
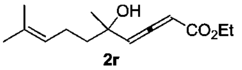
presence of an oxo-vanadium catalyst.[3] Alcaide observed the formation of mesylated 1,3-dienes upon treating allenic alcohols with methanesulfonyl chloride and triethylamine.[4a,b] Recently, the conversion of terminal allenic alcohols to 2-halo-1,3-dienes was observed in the presence of a stoichiometric amount of iron(III) halide.[4]

In our continued interest in allylic 1,3-transposition chemistry[5] coupled with functionalized 1,3-diene syntheses, we envisioned that the rearrangement of allenic alcohols shown in eq 3 should offer a unique opportunity not only for the exploration of their rearrangement under metal-catalyzed or metal-free conditions[6] but also for developing a new approach for stereoselective synthesis of functionalized 1,3-dienes. Previously reported typical syntheses of functionalized dienes involve metal-catalyzed coupling reactions,[7] elaborations of allenol derivatives[8] and vinyl ketones[9] but proceeded with poor selectivity, or were applied only to the synthesis of dienes with one terminal double bond.

In this regard, we envisioned that the significant thermodynamic driving force for the conversion of allenic alcohols to a substituted 1,3-dienes in eq 3 can be exploited to develop an efficient and stereoselective method for functionalized 1,3-dien-2-yl triflates and chlorides, which are versatile intermediates in organic synthesis. For example, these functionalized 1,3-dienes are viable building blocks to be engaged in a complex molecule synthesis[10] via Diels–Alder reactions and related cycloadditions. Recently, these dienyl triflates and halides were used as substrates for the preparation of chiral allenes.[11] Herein we report a general and stereoselective rearrangement of allenic alcohols to (*E,E*)-1,3-dien-2-yl triflates and chlorides under metal-free conditions where the subtle electronic effect of the alkyl and aryl substituents on the substrates has a profound impact on the reaction rate and efficiency.

Table 1. Synthesis of Allenyl Alcohols from Terminal Propargylic Alcohols and Ethyl Diazoacetate Catalyzed by CuI



entry	substrate	allenyl alcohol	yield (%)[a]
			
1	**1a** $R_1 = R_2 = H$	**2a**	90
2	**1b** $R_1 = Cl, R_2 = H$	**2b**	82
3	**1c** $R_1 = OMe, R_2 = OMe$	**2c**	80
4	**1d** $R_1 = H, R_2 = NO_2$	**2d**	81
5	 **1e**	 **2e**	81
6	 **1f**	 **2f**	74
7	 **1g**	 **2g**	76
8	 **1h**	 **2h**	83
9	 **1i**	 **2i**	79
			
10	**1j** R = Ph	**2j**	83
11	**1k** R = n-pentyl	**2k**	73
			
12	**1l** $R = CH_2CH_2Ph$	**2l**	85
13	**1m** R = n-pentyl	**2m**	78
14	**1n** R = cyclohexyl	**2n**	73
15	 **1o**	 **2o**	70
			
16	**1p** n = 1	**2p**	87
17	**1q** n = 7	**2q**	81
18	 **1r**	 **2r**	77

[a] Isolated yield after running the reaction at room temperature for 3 h followed by purification by flash chromatography.

First, by modifying the conditions for copper-catalyzed coupling of terminal alkynes **1a**–**r** and ethyl diazoacetate reported by Fu,[12] we optimized the synthesis of allenic alcohols **2a**–**r** (Table 1).[13] It was found that the addition of

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(3) (a) Trost, B. M.; Luan, X. *Nat. Protoc.* **2012**, *8*, 1497–1501. (c) Kalek, M.; Himo, F. *J. Am. Chem. Soc.* **2012**, *134*, 19159–19169.

(4) (a) Alcaide, B.; Almendros, P.; Aragoncillo, C.; Redondo, M. C. *Eur. J. Org. Chem.* **2005**, 98–106. (b) Alcaide, B.; Almendros, P.; Luna, A.; Prieto, N. *J. Org. Chem.* **2012**, *77*, 11388–11392.

(5) (a) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2006**, *128*, 8142–8143. (b) Volchkov, I.; Park, S.; Lee, D. *Org. Lett.* **2011**, *13*, 3530–3533. (c) Sun, C.; Li, J.; Lee, D.; Huang, G.; Xia, Y. *Chem. Commun.* **2012**, *48*, 10990–10992. (d) Huang, G.; Xia, Y.; Sun, C.; Li, J.; Lee, D. *J. Org. Chem.* **2013**, *78*, 988–995.

(6) Reviews on metal-free transformations: (a) Borisova, N. E.; Reshetova, M. D.; Ustynyuk, Y. A. *Chem. Rev.* **2007**, *107*, 46–79. (b) Barluenga, J.; Valdés, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 7486–7500. (c) Shao, Z.; Zhang, H. *Chem. Soc. Rev.* **2012**, *41*, 560–572.

(7) (a) Roush, W. R.; Moriarty, K. J.; Brown, B. B. *Tetrahedron Lett.* **1990**, *31*, 6509–6512. (b) Shen, W.; Wang, L. *J. Org. Chem.* **1999**, *64*, 8873–8879. (c) Ogasawara, M.; Ikeda, H.; Hayashi, T. *Angew. Chem., Int. Ed.* **2000**, *39*, 1042–1044.

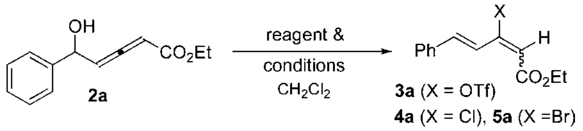
(8) (a) Deng, Y.; Fu, C.; Ma, S. *Org. Lett.* **2009**, *11*, 2169–2172. (b) Horvath, A.; Backvall, J.-E. *J. Org. Chem.* **2001**, *66*, 8120–8126.

(9) Ogasawara, M.; Ge, Y.; Uetake, K.; Takahashi, T. *Org. Lett.* **2005**, *7*, 5697–5700.

(10) (a) Johnson, W. S.; Telfer, S. J.; Cheng, S.; Schubert, U. *J. Am. Chem. Soc.* **1987**, *109*, 2517–2518. (b) Schreiber, S. L.; Kiessling, L. L. *J. Am. Chem. Soc.* **1988**, *110*, 631–633.

(11) (a) Ogasawara, M.; Ikeda, H.; Nagano, T.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 2089–2090. (b) Ogasawara, M.; Nagano, T.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 5764–5767.

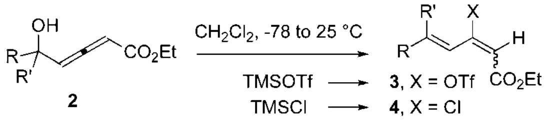
Table 2. Reagent Screening for 1,3-Transposition

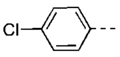
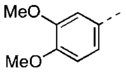
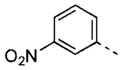
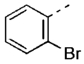
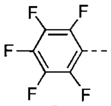
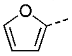
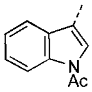
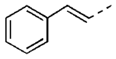
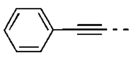
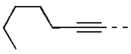
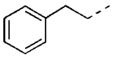
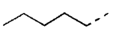
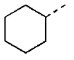
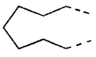
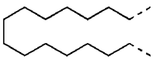
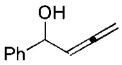
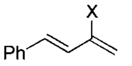


entry	reagent	equiv	temp (°C)	time (h)		yield (%)[a]	*E*/*Z*[b]
1	TMSOTf	1	rt	1	**3a**	53[c]	1:0
2	TMSOTf	2	rt	0.5	**3a**	63	1:0
3	TMSOTf	2	−78 to rt	0.5	**3a**	77	1:0
4	TMSCl	1	rt	2	**4a**	65[d]	35:1
5	TMSI	3	rt	1	**4a**	89	33:0
6	$POCl_3$	1	rt	2	**4a**	35	1:0
7	TMSBr	1	rt	0.5	**5a**	–[e]	–
8	TMSBr	1	−78	0.5	**5a**	92	14:1
9	PBr_3	1	rt	1	**5a**	78	1:1

[a] Isolated yield. [b] *E*/*Z* ratio was determined by ^{1}H NMR, and the stereochemistry of the products was determined by ^{1}H NOE. [c] Only 70% conversion, and the yield is based on recovered starting material. [d] Only 45% conversion, and the yield is based on recovered starting material. [e] Decomposition of **2a**.

Table 3. Scope of the Allylic 1,3-Transposition with TMSOTf and TMSCl



entry		R	R'	product	yield (%)[a]	*E*:*Z*[b]
1	**2b**		H	**3b** **4b**	89 87	1:0 1:0
2	**2c**[c]		H	**3c** **4c**	— 93	— 19:1
3	**2d**[d]		H	**3d** **4d**	83 —[e]	1:0 —
4	**2e**		H	**3e** **4e**	81 —[f]	1:0 —
5	**2f**[d]		H	**3f** **4f**	74 —	20:1 —
6	**2g**[c]		H	**3g** **4g**	— 84	— 16:1
7	**2h**[c]		H	**3h** **4h**	— 81	— 1.5:1
8	**2i**		H	**3i** **4i**	71 91	10:1 5:1
9	**2j**[g]		H	**3j** **4j**	72 —	5:1 —
10	**2k**[g]		H	**3k** **4k**	77 —	3.5:1 —
11	**2l**[d]		H	**3l** **4l**	76 —[h]	10:1 —
12	**2m**[d]		H	**3m** **4m**	74 —[h]	20:1 —
13	**2n**[d]		H	**3n** **4n**	77 —[h]	20:1 —
14	**2o**[c]	Me	Me	**3o** **4o**	— 67[i]	— 1:0
15	**2p**[c]			**3p** **4p**	— 56[i]	— 1:0
16	**2q**[c]			**3q** **4q**	— 63[i]	— 1:0
17	**2s**				**3s** 81 (X = OTf)[j] **4s** 72 (X = Cl)	

[a] Isolated yields. [b] *E*/*Z* ratio was determined by ^{1}H NMR, and the stereochemistry was determined by NOE. [c] Decomposition with TMSOTf. [d] No reaction with TMSCl. [e] After heating up to 150 °C, **2d** was recovered (70%). [f] Unknown product was formed. [g] Decomposition with TMSCl. [h] Very low conversion even with 5 equiv of TMSCl. [i] Excess TMSCl (5 equiv) was used for full conversion. [j] During the purification, vinyl triflate **3s** hydrolyzed to *trans*-4-phenyl-3-buten-2-one.

a stoichiometric amount of triethylamine to the reaction effectively isomerized the alkynyl alcohols to the corresponding allenic alcohols in excellent yield regardless of the nature of the substituents. Because of the secondary alcohol and disubstituted allene stereogenic units, these allenic alcohols were obtained as a mixture of diastereomers (1:1). In addition, it was found that the hydroxyl group at the propargylic center plays an important role in facilitating the isomerization of the alkyne to the allene. Under the same conditions, terminal alkynes without the hydroxyl group provided a mixture of the alkyne- and allene-containing coupled products.[14]

Next, we examined the allylic transposition of allenic alcohol **2a** under various metal-free conditions employing TMSOTf, TMSCl, $POCl_3$, TMSBr, and PBr_3 (Table 2). Treatment of allenic alcohol **2a** with TMSOTf (1 equiv) at room temperature for 1 h provided vinyl triflate **3a** as a single isomer in 53% yield (entry 1). The yield of **3a** was increased to 63% with 2 equiv of TMSOTf for 0.5 h (entry 2), and further up to 77% by running the reaction at lower temperature (entry 3). Reactions with TMSCl provided vinyl chloride **4a** with good selectivity in 65% yield (*E*/*Z* = 35:1) after 2 h (based on 45% conversion) when 1 equiv of the reagent was employed (entry 4). The yield of **4a** increased to 89% (*E*/*Z* = 33:1) with 3 equiv of TMSCl (entry 5). A single isomer of vinyl chloride **4a** could be obtained from the reaction with $POCl_3$ but only in 35%

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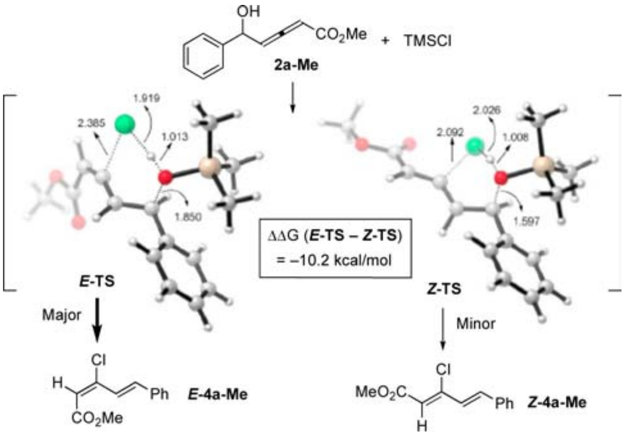
yield (entry 6). While a more reactive reagent such as TMSBr rendered the decomposition of the substrate at room temperature, the expected bromide **5a** was obtained in good yield and selectivity at −78 °C (entries 7 and 8). Also the reaction with PBr_3 afforded **5a** in 78% yield as a mixture of *E*/*Z*-isomers in a 1:1 ratio (entry 9). In all cases, the 1,3-diene products are trans in the styryl unit.

In order to extend the scope of this rearrangement, a variety of allenic alcohols were treated with TMSOTf and TMSCl and the results are shown in Table 3. When treated with both TMSOTf and TMSCl, substrates **2b** and **2i** with the 4-chlorophenyl and cinnamyl group afforded dienyl triflate **3b**/**3i** and dienyl chloride **4b**/**4i**, respectively, with good yields and *E*/*Z*-selectivity (entries 1 and 8). However, allenic alcohols **2d**−**f** possessing electron-withdrawing groups on the aromatic ring (entries 4−6) or **2j**/**2k** containing alkynyl substituents (entries 9 and 10), showed good reactivity profiles with TMSOTf, yielding the corresponding dienyl triflates **3d**−**f** and **3j**/**3k** in good yields, but were found to be inert (**2d**, **2f**, **2j**, **2k**) or afforded an unidentified material (from **2e**) with TMSCl. Interestingly, only the alkyne-substituted substrates **3j** and **3k** showed relatively low *E*/*Z*-selectivity (5:1 and 3.5:1). On the other hand, upon increasing the electron-donating nature of the aryl/heteroaryl groups such as in allenic alcohols **2c**, **2g**, and **2h** (entries 2, 6, and 7), the opposite reactivity profiles were observed, where the decomposition of substrates was observed with TMSOTf, yet excellent yields and selectivity of dienyl chlorides **4c**, **4g**, and **4h** were obtained with TMSCl with the exception of the low selectivity of **4h** (*E*/*Z* = 1.5:1). Secondary allenic alcohols **2l**−**n** with either cyclic or acyclic alkyl substituents (entries 11−13) reacted with TMSOTf to deliver dienyl triflates **3l**−**n** in good yields and selectivity, but they are virtually inert with TMSCl. On the other hand, tertiary allenic alcohols **2o**−**q** (entries 14−16) decomposed with TMSOTf yet provided *E*-dienyl chlorides **4l**−**n** in acceptable yields. A terminal allenic alcohol **2s** without an ester group afforded the corresponding dienyl triflate **3s** and chloride **4s** upon treatment with TMSOTf and TMSCl, respectively (entry 17). These results clearly demonstrate the need for a delicate balance of the electronic effect of the substituents in the substrates and reactivity of TMSOTf and TMSCl for the observed 1,3-transposition.[15]

To gain insight into the mechanism, we carried out brief DFT caculations (M06-2X/6-31G*/PCM Level) for the transition state (TS) of the 1,3-rearrangement of **2a-Me** (methyl ester equivalent of **2a**) with TMSCl (Scheme 2). The calculated TSs show that the rearrangement occurring with hydrogen bonded intramolecular delivery of a chloride ion is the most favorable reaction pathway. The *E*/*Z*-selectivity can be rationalized by the more favorable transition state ***E*-TS**, where the approach of a chloride ion is from the side of the hydrogen as opposed to that of the methoxycarbonyl group in ***Z*-TS**, generating ***E*-4a-Me** predominantly. The energy difference between these two TSs (−10.2 kcal/mol) is consistent with the observed high *E*/*Z*-selectivity in the product. On the basis of this model calculation, we surmise that the 1,3-transpositions of other substrates induced by TMSOTf and TMSBr also proceed through a similar mechanism. The six-membered ring TSs also can explain the lack of products without the 1,3-position in these reactions.

Scheme 2. DFT-Calculated TSs of 1,3-Transposition of **2a-Me** with TMSCl (M06-2X/6-31G*/PCM Level; Distances are in Å)



In summary, an efficient metal-free rearrangement of allenic alcohols bearing aromatic, conjugated, or aliphatic substituents to the corresponding 1,3-dienyl triflates and chlorides has been developed by using TMSOTf and TMSCl. Clearly, the driving force of this 1,3-transposition is the formation of more stable conjugated dienes. The effective synthesis of tri- and tetrasubstituted 1,3-dienes with excellent *E*/*Z*-selectivity by instituting the sequential formation of allenic alcohols from readily available building blocks followed by their rearrangement under metal-free conditions makes this process synthetically valuable.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] A related example with the corresponding vinylogous system: Jiang, H.; Gao, Y.; Wanqing, W.; Huang, Y. *Org. Lett.* **2013**, *15*, 238–241.

The authors declare no competing financial interest.