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Negishi Coupling between α-Alkyl(aryl)thio Vinyl Zinc Chloride and α-Bromo Vinyl Ether: A Convergent Synthesis of 2-Alkoxy-3-alkyl(aryl)thiobuta-1,3-dienes[1]

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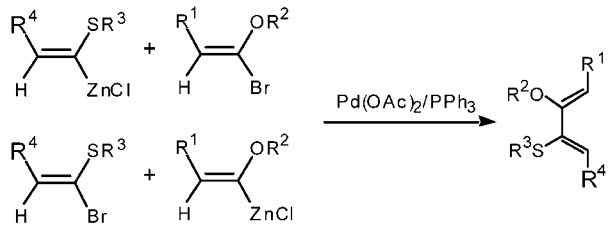
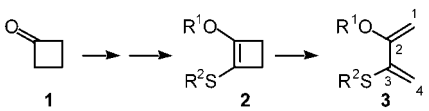
ABSTRACT



A convergent approach for the stereoselective synthesis of 2-alkoxy-3-alkyl(aryl)thiobuta-1,3-dienes has been developed. It was found that Negishi coupling between α-alkyl(aryl)thio vinyl zinc chloride and α-bromo vinyl ether or Negishi coupling between α-bromo vinyl sulfide and α-alkoxy vinyl zinc chloride provided the best yield and stereoselectivity.

Heteroatom-substituted 1,3-dienes play a very important role in cycloadditions. The introduction of heteroatom functional groups to 1,3-dienes can control both regio- and stereoselectivity in cycloadditions. For example, Danishefsky developed 1-methoxy-3-trimethylsiloxybuta-1,3-diene which has led to many creative applications in complex organic synthesis.[2] Trost and co-workers developed another kind of 1,3-diene, 2-alkoxy-3-alkyl(aryl)thiobuta-1,3-diene **3**, which has been used as a regiochemical control element in cycloadditions.[3] According to Trost's procedures, compound **3** was prepared from cyclobutanone (Scheme 1).[3] Although this is a novel approach, some limitations still exist. For instance, the synthetic route is tedious, and it is difficult to prepare 1,3-dienes with substituents at the 1 and 4 positions. Therefore, we decided to develop a new procedure for the stereoselective synthesis of a variety of 2-alkoxy-3-alkyl-(aryl)thiobuta-1,3-dienes with different substituents on both the 1 and 4 positions.

Scheme 1



(1) Synthesis via α-halo vinyl ethers. 4.
(2) Danishefsky, S. J. *Aldrichimica Acta* **1986**, *19*, 59 and references therein.
(3) (a) Trost, B. M.; Bridges, A. J. *J. Am. Chem. Soc*. **1976**, *98*, 5017. (b) Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc.* **1980**, *102*, 3548. (c) Trost, B. M.; Vladuchick, W. C.; Bridges, A. J. *J. Am. Chem. Soc*. **1980**, *102*, 3554.

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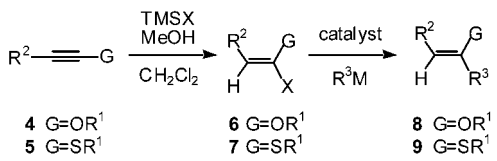
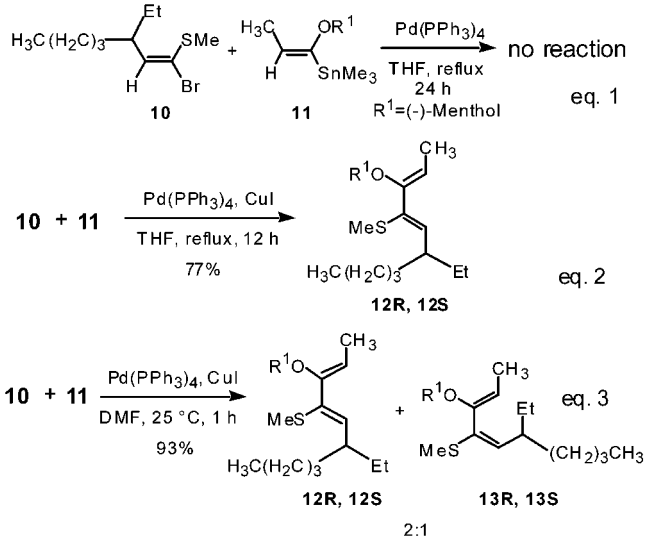
Scheme 2



Recently, we discovered that hydrogen halide generated in situ (by reaction of trimethylsilyl halide with anhydrous methanol) can add to acetylenic ethers at low temperature in a completely regio- and stereoselective manner with nearly quantitative yields (Scheme 2).[4] This methodology was successfully extended to the stereoselective synthesis of α-halo vinyl sulfides.[5] Furthermore, we also demonstrated that both α-halo vinyl ethers and α-halo vinyl sulfides are versatile substrates for many important transformations such as transition metal catalyzed cross-coupling reactions.[4,5] This motivated us to investigate the possibility of the development of a convergent approach for the stereoselective synthesis of 2-alkoxy-3-alkyl(aryl)thiobuta-1,3-dienes.

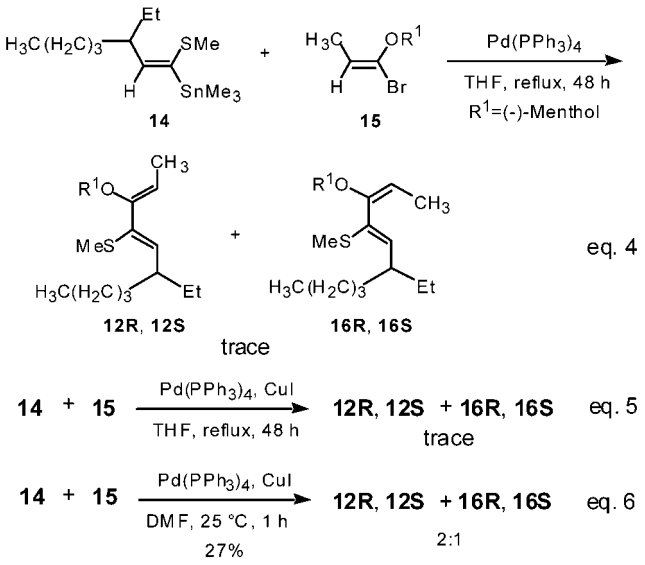
We first studied the Stille coupling[6] between α-bromo vinyl sulfide **10** and α-alkoxy vinyl stannane **11**, which was derived from α-alkoxy vinyllithium on the basis of our methodology (Scheme 3).[4] Under the typical Stille conditions, no reaction was observed after the reaction mixture was heated at reflux for 24 h (Scheme 3, eq 1). With the addition of cocatalyst CuI,[7] the reaction occurred in THF, but it was still quite slow and never went to completion even with the addition of 0.75 equiv of CuI (Scheme 3, eq 2). After heating at reflux for 12 h, compounds **12R** and **12S** were isolated in 77% yield along with the recovery of 20% of the starting material **11**.[8] When the solvent was replaced with DMF (Scheme 3, eq 3), the reaction was much faster and was complete in 1 h at 25 °C. However, the stereochemistry of the double bond was not retained, and compounds **13R** and **13S** were also formed in 31% yield.[8]

Scheme 3



We then investigated the Stille coupling between α-alkylthio vinyl stannane **14**[5] and α-bromo vinyl ether **15**. The results are summarized in Scheme 4. More than 90% of the starting materials was recovered from both reactions (eq 4 and eq 5), and only a trace amount of the products was isolated.[8] Even in the presence of CuI and DMF, the reaction was still very slow and not stereoselective (eq 6).[8] These experimental results suggest that Stille coupling is not the method of choice for the stereoselective synthesis of 2-alkoxy-3-alkylthiobuta-1,3-dienes. Another coupling reaction was needed to achieve high yield and excellent stereoselectiveity.

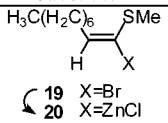
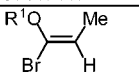
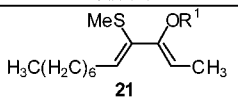
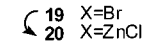
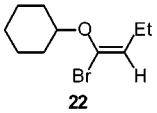
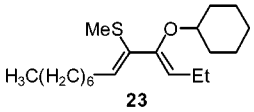
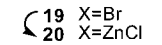
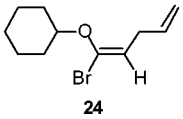
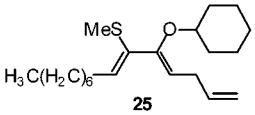
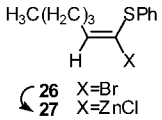
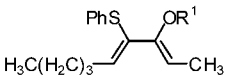
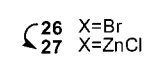
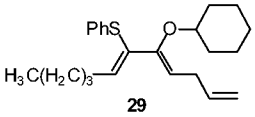
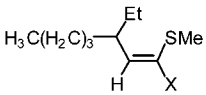
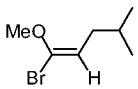
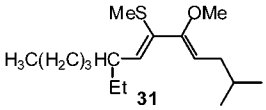
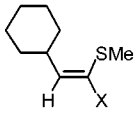
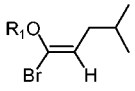
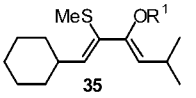
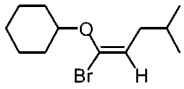
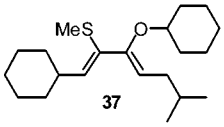
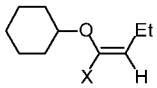
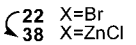
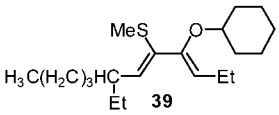
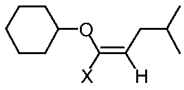
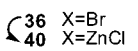
Scheme 4



It is known that the vinyl zinc chloride reagents used in Negishi couplings are generally more reactive than the corresponding vinyl stannane.[9] So compound **10** was con-

(4) Yu, W.; Jin, Z. *J. Am. Chem. Soc.* **2000**, *122*, 9840.
(5) Su, M.; Yu, W.; Jin, Z. *Tetrahedron Lett.* **2001**, *42*, 3771.
(6) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Org. React.* **1997**, *50*, 1 and references therein.
(7) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905 and references therein.
(8) The geometry of the double bonds was determined by NOESY spectra. The *E*/*Z* ratios were measured by integration of well-resolved signals in the corresponding ^{1}H NMR.
(9) (a) King, A. O.; Okukado, N.; Negishi, E.-i. *Chem. Commun.* **1977**, 683. (b) Negishi, E.-i.; Okukado, N.; King, A. O.; Van Horn, D. E.; Spiegel, B. I. *J. Am. Chem. Soc.* **1978**, *100*, 2254. (c) Negishi, E.; Luo, F.-T. *J. Org. Chem.* **1983**, *48*, 1560. (d) Negishi, E.-i.; Bagheri, V.; Chatterjee, S.; Luo, F.-T. *Tetrahedron Lett.* **1983**, *24*, 5181. (e) Negishi, E.-i.; Takahashi, T.; Baba, S.; Van Horn, D. E.; Okukado, N. *J. Am. Chem. Soc.* **1987**, *109*, 2393.

Table 1. Synthesis of 2-Alkoxy-3-alkyl(aryl)thiobuta-1,3-dienes

Entry[a]	Substrate 1	Substrate 2[b]	Products[c]	Yield[d]
1	 **19** X=Br, **20** X=ZnCl	 **15**	 **21**	86%
2	 **19** X=Br, **20** X=ZnCl	 **22**	 **23**	91%
3	 **19** X=Br, **20** X=ZnCl	 **24**	 **25**	83%
4	 **26** X=Br, **27** X=ZnCl	**15**	 **28**	91%
5	 **26** X=Br, **27** X=ZnCl	**24**	 **29**	87%
6	 **10** X=Br, **17** X=ZnCl	 **30**	 **31**	80%
7	 **32** X=Br, **33** X=ZnCl	 **34**	 **35**	70%
8	**32** X=Br, **33** X=ZnCl	 **36**	 **37**	73%
9	**10**	  **22** X=Br, **38** X=ZnCl	 **39**	85%
10	**32**	  **36** X=Br, **40** X=ZnCl	**37**	75%

[a] All reactions were run in either ether or toluene at 25 °C. [b] R^1 = (−)-menthol. [c] The geometry of double bonds were determined by NOESY spectra. The minor isomer was not detected by NMR. [d] All yields are isolated yields.

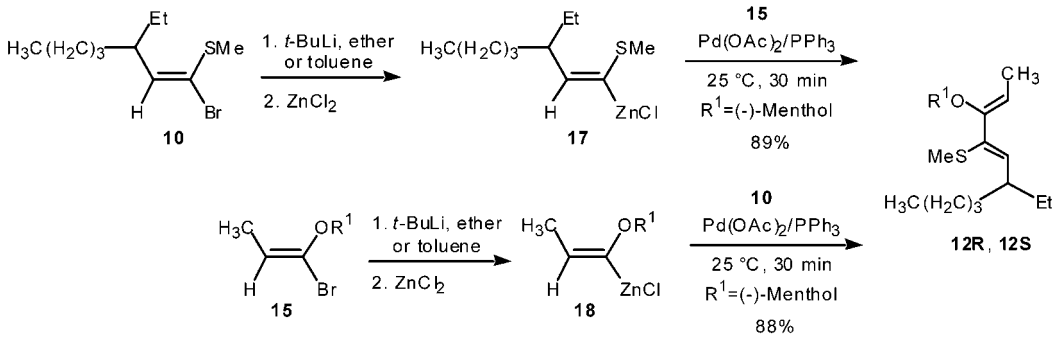
verted to α-alkylthio vinyl zinc chloride intermediate **17** by reaction with *t*-BuLi followed by transmetalation with anhydrous $ZnCl_2$ (Scheme 5). Under the Negishi conditions, compound **17** reacted with α-bromo vinyl ether **15** to provide the desired compounds **12R** and **12S**. The reaction was complete in 30 min at 25 °C and the stereoselectivity was excellent.[10] Under the same conditions, compound **18** reacted with compound **10** to afford compounds **12R** and **12S** in 88% yield with complete stereoselectivity.[10] Table 1 summarizes the preparation of a variety of 2-alkoxy-3-alkylthiobuta-1,3-dienes using our procedures.[11]

In conclusion, we have successfully developed a convergent and highly stereoselective synthesis of 2-alkoxy-3-alkylthiobuta-1,3-dienes. We have shown that the coupling reactions between α-alkylthio vinyl zinc with α-halo vinyl ether under Negishi conditions provided the best yield and

(10) The minor isomer was not detected by NMR.

(11) All compounds were fully characterized.

Scheme 5



stereoselectivity. Once again, this further demonstrated the high versatility of both α-halo vinyl ether and α-halo vinyl sulfide chemistry.

Acknowledgment. This work was supported by Grant IN-122S from the American Cancer Society, administered through The University of Iowa Cancer Center, a Research Project Grant RPG-00-030-01-CDD from the American Cancer Society, and the Central Investment Fund for Research Enhancement (CIFRE) at The University of Iowa. Special thanks are due to The Center for Biocatalysis and Bioprocessing at The University of Iowa for providing a fellowship to W. Yu.

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

OL010252K

(12) **Typical Procedure for the Convergent Synthesis of 2-Alkoxy-3-alkyl(aryl)thiobuta-1,3-dienes:** To a solution of α-bromo vinyl sulfide (1.5 mmol) in anhydrous ether (3 mL) was added *t*-BuLi (3.0 mmol) at −78 °C. The reaction mixture was stirred at −78 °C and monitored by TLC until the disappearance of the α-bromo vinyl sulfide. Anhydrous $ZnCl_2$ in ether (1.5 mmol, 1.0 M)) was added, and the reaction mixture was warmed to 0 °C. A solution of α-bromo vinyl ether (1.0 mmol), $Pd(OAc)_2$ (0.05 mmol), and PPh_3 (0.1 mmol) in anhydrous ether was then added via a cannula. The reaction mixture was stirred at 25 °C until TLC showed the disappearance of α-bromo vinyl ether. After removal of the solvent, the desired product 2-alkoxy-3-alkylthiobuta-1,3-diene was purified by flash column chromatography.