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Titanium(IV) Halide Mediated Coupling of Alkoxides and Alkynes: An Efficient and Stereoselective Route to Trisubstituted (*E*)-Alkenyl Halides

Min-Liang Yao, Travis R. Quick, Zhongzhi Wu, Michael P. Quinn, and George W. Kabalka*

Departments of Chemistry and Radiology, The University of Tennessee, Knoxville, Tennessee 37996-1600

kabalka@utk.edu

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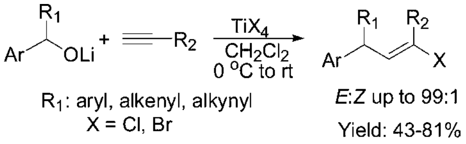
ABSTRACT

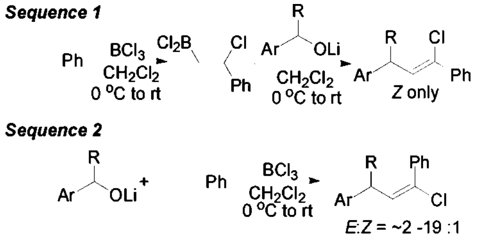


Alkoxide C−O bond cleavage occurs readily at room temperature in the presence of titanium(IV) halide. Capture of the resultant carbocation by alkynes provides an efficient route to trisubstituted (*E*)-alkenyl halides with high stereoselectivity.

In 2005, we reported the first transition-metal-free nucleophilic substitution of hydroxyl groups, through the corresponding alkoxides, by stereodefined haloalkenyl moieties (Scheme 1).[1,2] The reaction involves the unprecedented C−O bond cleavage of an alkoxide in the presence of halovinylboron dihalide and provides a practical route to trisubstituted (*Z*)-alkenyl halides. The reaction proceeds quite well with alkoxides generated in situ from reactions of aldehydes and alkyllithium reagents which further adds versatility to the method.[1b,3]

During ongoing mechanistic studies of the aldehyde-alkyne coupling reaction,[4] we discovered that changing the mode of reagent addition greatly affects the stereochemistry of the product formed. Thus, coupling alkoxides with terminal alkynes in the presence of boron trihalide yields trisubstituted (*E*)-alkenyl halides as the major products with moderate stereoselectivities[5] (Scheme 1). In these cases, we believe that carbocations are generated from alkoxides in the presence of boron trihalide and subsequently captured by the terminal alkynes.

Scheme 1. Swift Stereochemistry via Changing Reactant Adding Sequence



Our recent study of boron tribromide-mediated aryl propargyl ether cleavage[6] suggests that the addition of boron trihalide to terminal alkynes is a very fast process. Methoxy groups (known to react with BBr_3) were found to survive the reaction conditions

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(1) (a) Kabalka, G. W.; Yao, M.-L.; Borella, S.; Wu, Z.-Z. *Chem. Commun.* **2005**, 2865. (b) Kabalka, G. W.; Yao, M.-L.; Borella, S.; Wu, Z.-Z. *Org. Lett.* **2005**, *7*, 2865.

(2) Recent reports related to transition-metal-free nucleophilic substitution of hydroxyl groups with alkenyl moieties. See: (a) Morgan, I. R.; Yazici, A.; Pyne, S. G. *Tetrahedron* **2008**, *64*, 1409. (c) Nishimoto, Y.; Kajioka, M.; Saito, T.; Yasuda, M.; Baba, A. *Chem. Commun.* **2008**, 6396.

(3) Kabalka, G. W.; Yao, M.-L.; Borella, S. *Org. Lett.* **2006**, *8*, 879.

(4) Kabalka, G. W.; Yao, M.-L.; Borella, S.; Wu, Z.-Z.; Ju, Y.-H.; Quick, T. *J. Org. Chem.* **2008**, *73*, 2663.

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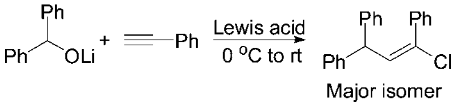
because of the high reactivity of BBr_3 toward the terminal alkynes. This observation led us to propose that the moderate stereoselectivity for the reaction shown in Sequence 2 (Scheme 1) resulted from a competitive reaction involving the facile formation of (*Z*)-vinylboron dihalide (giving the *Z*-isomer after coupling with the alkoxide). To minimize this undesired competitive reaction, we felt that replacement of boron trihalide with Lewis acids that do not undergo facile addition to alkynes might enhance the stereoselectivity of the overall coupling reaction. Previous studies from our group,[7] as well as other groups,[8] have demonstrated that C−O bond cleavage in alkoxide-type $RC-OMX_n$ (M = Ti, Fe) intermediates can occur smoothly at room temperature. In 2008, Fuchter and Levy reported a one-pot method for the conversion of carbonyl electrophiles to allylic chlorides by activating the *in situ* generated magnesium alkoxides using $TiCl_4$.[9] Related work by Murai and co-workers documented successful C−S bond cleavage.[10] Herein we report our preliminary results focused on the stereoselective synthesis of trisubstituted (*E*)-alkenyl halides.

The reaction of lithium diphenylmethanoxide with phenylacetylene was chosen as the model system (Scheme 2).

Scheme 2. Lewis Acid Induced Coupling Reaction



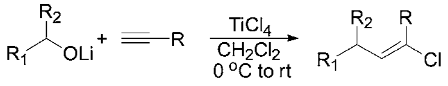
Lewis acid: $FeCl_3$, $TiCl_4$, $ZnCl_2$, $NiCl_2$

Due to its low cost, $FeCl_3$ was initially used to test the feasibility of the coupling reaction.

Several solvents were surveyed but the poor solubility of $FeCl_3$ led to modest yield even after 24 h at room temperature. Elevating the reaction temperature did increase the yield but led to decreased stereoselectivity. These results are consistent with a recent publication concerning the $FeCl_3$ mediated coupling of benzyl alcohols and aryl alkynes in refluxing CH_2Cl_2 which reports the formation of trisubstituted (*E*)-alkenyl halides as the major products but with only moderate stereoselectivities ($E/Z = \sim 8:1$).[11] Notably, in 2008 Jana et al. reported that the $FeCl_3$ mediated reaction in nitromethane at 80 °C gives aryl ketones, rather than trisubstituted (*E*)-alkenyl halides.[12] Due to the poor solubility of $FeCl_3$ in organic solvents at room temperature, we decided to screen other metal halides. Fortunately, the desired reaction occurred smoothly at room temperature using $TiCl_4$; product **1a** was isolated in 78% yield and with excellent stereoselectivity (E/Z = 96:4).[13] $ZnCl_2$ and $NiCl_2$ proved to be ineffective. The product's *E* stereochemistry was confirmed by X-ray analysis of compound **1d**.[14]

To evaluate the scope and limitations of the reaction, a variety of benzylic, allylic, and propargylic alcohols were prepared and subjected to the new reaction conditions (Table 1). Several examples illustrate that ether moieties, double bonds, and triple bonds all tolerate the reaction conditions. The *E* products are produced in excellent stereochemical yields.[15] Even lithium di(4-fluorobenzyl)methanoxide gives excellent stereoselectivity (entry 5) using $TiCl_4$. In our previous work, this reaction afforded very poor stereoselectivity (E/Z = 60:40) when BCl_3 was used.[5] Successful coupling using an aliphatic alkyne is notable, though the stereoselectivity is rather poor (E/Z = 70:30, entry 7). In recent reports,[11,12] it was noted that the $FeCl_3$ mediated coupling reaction of benzylic alcohols with alkynes is only successful for aryl alkynes. The lower stereoselectivity (E/Z) for aliphatic alkynes is most likely due to the lack of steric bulk of the *n*-butyl group.

Table 1. Titanium(IV) Chloride Mediated Coupling of Alkoxides with Alkynes[a]



Entry	R_1	R_2	R	prod.	*E*:*Z*	yield (%)[c]
1	Ph	Ph	Ph	**1a**	96:4 (90:10)[d]	78 (84)[d]
2	2-MeC_6H_4	Ph	Ph	**1b**	99:1	58
3	4-FC_6H_4	4-FC_6H_4	Ph	**1c**	98:2 (60:40)[d]	81 (80)[d]
4	4-ClC_6H_4	Ph	4-MeC_6H_4	**1d**	96:4	76
5	4-FC_6H_4	4-FC_6H_4	4-MeC_6H_4	**1e**	98:2	76
6	4-$MeOC_6H_4$	4-$MeOC_6H_4$	Ph	**1f**	92:8	43
7	Ph	Ph	*n*-Bu	**1g**	70:30	62
8	(*E*)-PhCH=CH	Ph	Ph	**1h**	99:1	68
9	*n*-Bu—≡	4-ClC_6H_4	Ph	**1i**	99:1	68
10	*n*-Bu—≡	4-MeC_6H_4	Ph	**1j**	99:1	67
11	Ph—≡	Ph	Ph	**1k**	98:2	75
12	Ph—≡	*n*-Pr	Ph	**1l**	96:4	71

[a] Reaction was carried out at 0 °C for 10 min, then maintained at room temperature (see experimental section for details). [b] *E*:*Z* ratio determined by NMR. [c] Isolated yield based on alcohol. [d] *E*:*Z* stereoselectivity and yield using BCl_3 instead of $TiCl_4$.

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(5) Kabalka, G. W.; Yao, M.-L.; Borella, S. *J. Am. Chem. Soc.* **2006**, *128*, 11320.

(6) Yao, M.-L.; Reddy, M. S.; Zeng, W.-b.; Hall, K.; Walfish, I.; Kabalka, G. W. *J. Org. Chem.* **2009**, *74*, 1385.

(7) (a) Kabalka, G. W.; Yao, M.-L.; Borella, S.; Goins, L. K. *Organometallics* **2007**, *26*, 4112. (b) Kabalka, G. W.; Ju, Y.; Wu, Z. *J. Org. Chem.* **2003**, *68*, 7915. (c) Kabalka, G. W.; Wu, Z.; Ju, Y. *Org. Lett.* **2002**, *4*, 3415.

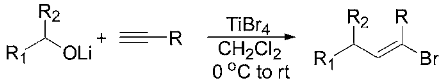
(8) (a) Karunakar, G. V.; Periasamy, M. *J. Org. Chem.* **2006**, *71*, 7463. (b) Falck, J. R.; Bejot, R.; Barma, D. K.; Bandyopadhyay, A.; Joseph, S.; Mioskowski, C. *J. Org. Chem.* **2006**, *71*, 8178. (c) Miranda, P. O.; Diaz, D. D.; Padron, J. I.; Ramirez, M. A.; Martin, V. S. *J. Org. Chem.* **2005**, *70*, 57.

(9) Fuchter, M. J.; Levy, J.-N. *Org. Lett.* **2008**, *10*, 4919.

(10) (a) Murai, T.; Asai, F. *J. Org. Chem.* **2008**, *73* (2), 9518. (b) Murai, T.; Asai, F. *J. Am. Chem. Soc.* **2007**, *129*, 780.

Because of the synthetic potential of alkenyl bromides in transition metal catalyzed coupling reactions, we examined the use of $TiBr_4$ (Table 2). Again, the reaction proceeds readily at room temperature and good yields are obtained. We then examined the reactions of in situ generated lithium propargyloxides (from aryl aldehydes and lithium acetylide) with phenylacetylene (entries 4 and 5). High stereoselectivity and good yields were obtained in both cases.

Table 2. Titanium(IV) Bromide Mediated Coupling of Alkoxides with Alkynes[a]

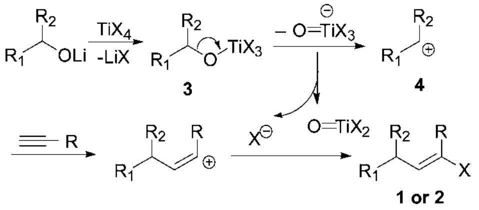


Entry	R_1	R_2	R	prod	E:Z[b]	yield (%)[c]
1	4-MeOC_6H_4	4-MeOC_6H_4	4-MeC_6H_4	**2a**	96:4	59
2	4-MeOC_6H_4	4-MeOC_6H_4	Ph	**2b**	96:4	64
3	Ph	Ph	4-MeC_6H_4	**2c**	98:2	79
4[d]	Ph—≡	Ph	Ph	**2d**	99:1	74
5[d]	*n*-Bu—≡	Ph	Ph	**2e**	99:1	76
6	*n*-Bu—≡	Ph	4-MeC_6H_4	**2f**	99:1	66
7	*n*-Bu—≡	4-ClC_6H_4	Ph	**2g**	98:2	66

[a] Reaction was carried out at 0 °C for 10 min, then maintained at room temperature (see experimental for details). [b] E:Z ratio determined by NMR. [c] Isolated yield based on alcohol used. [d] Lithium alkoxide was generated *in situ* from the reaction of benzaldehyde and lithium acetylide.

In view of the previously reported results[4,5] along with the dark purple color of reaction mixture, we postulate that the reactions proceed through a carbocation mechanism (Scheme 3). The reaction of the lithium alkoxide with TiX_4 first forms intermediate **3** [$R_1R_2CHO{-}TiCl_3$]. Carbocation **4** is then generated from either intermediate [$R_1R_2CHO{-}TiCl_3$] or an oxonium ion intermediate [$R_1R_2CHO{-}(TiCl_4)TiCl_3$].[16] At present, there is insufficient data available to distinguish between these two pathways. Capture of carbocation **4** by the alkyne affords final product **1** or **2**. The carbocation nature of the reaction is supported by compounds **1** and **2** possessing the same stereochemistry with compounds that were obtained in a previously reported reaction of benzylic carbocations with alkynes.[17]

Scheme 3. Proposed Reaction Mechanism



In summary, a method for preparing trisubstituted (E)-alkenyl halide derivatives with high stereoselectivity is described. Both trisubstituted (E)-alkenyl halide and (Z)-alkenyl halide derivatives can now be prepared from readily available alkoxides and acetylenes. The feasibility of generating carbocations from alkoxides under Brønsted acid-free reaction conditions was further confirmed. Application of this new synthetic method is currently underway.

Acknowledgment. Acknowledgement is made to the Donors of the American Chemical Society Petroleum Research Fund for partial support of this research. We also wish to thank the U.S. Department of Energy, and the Robert H. Cole Foundation.

Supporting Information Available: ^1H and ^{13}C NMR data for all new compounds reported, X-ray data for compound **1d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) During the preparation of this manuscript, the $FeCl_3$ mediated coupling reaction of alcohols with alkynes in refluxing CH_2Cl_2 was reported. The low stereoselectivity, we believe, is due to the enhanced reaction temperature. Liu, Z.-Q.; Wang, J.; Han, J.; Zhou, B. *Tetrahedron Lett.* **2009**, *50*, 1240.

(12) Jana, U.; Biswas, S.; Maiti, S. *Eur. J. Org. Chem.* **2008**, 5798.

(13) Typical reaction procedure: Diphenylmethanol (276 mg, 1.5 mmol) and dichloromethane (15 mL) were placed in a dry, argon-flushed, 100 mL round-bottomed flask equipped with a magnetic stirring bar. The solution was cooled to 0 °C in an ice bath and n-butyllithium (1.6 mmol, 1.6 mL of a 1.0 M hexanes solution) was added via syringe. The solution was allowed to stir for 10 minutes at 0 °C and then for 30 minutes at room temperature. Phenylacetylene (0.16 mL, 1.5 mmol) was added via syringe, followed by titanium(IV) chloride (1.65 mmol, 1.65 mL of a 1.0 M dichloromethane solution). The reaction solution gradually turned dark purple and was allowed to react overnight. The resulting mixture was hydrolyzed with water (15 mL) and extracted into dichloromethane (3 × 15 mL). The organic layer was separated and dried over anhydrous $MgSO_4$. Product **1a** (356 mg, $E/Z = 96{:}4$, 78% yield) was isolated by flash column chromatography, using hexanes as eluent.

(14) For details of the crystallographic data of compound **1d**, see Supporting Information.

(15) The stereoselectivity can be readily determined using 1H NMR since the resonances for vinyl protons and allylic protons in the E-isomer and Z-isomer are quite different. Generally, the allylic proton in the E-isomer appears near 4.80 ppm, whch is upfield compared to the corresponding proton in the Z-isomer (generally found near 5.40 ppm).

(16) Forming carbocations from an oxonium ion intermediate [$R_1R_2CHO{-}(MCl_n)MCl_{n-1}$], see: (a) Kabalka, G. W.; Yao, M.-L.; Borella, S.; Quick, T. *J. Chem. Soc.: Dalton Trans.* **2008**, 776. (b) Kim, S. H.; Shin, C.; Pae, A. N.; Koh, H. Y.; Chang, M. H.; Chung, B. Y.; Cho, Y. S. *Synthesis* **2004**, 1581. (c) Yokozawa, T.; Furuhashi, K.; Natsume, H. *Tetrahedron Lett.* **1995**, *36*, 5243. (d) Braun, M.; Kotter, W. *Angew. Chem., Int. Ed.* **2004**, *45*, 1514.

(17) Marcuzzi, F.; Melloni, G.; Modena, G. *J. Org. Chem.* **1979**, *44*, 3022.