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2-Bromoallyl Acetate: A Useful Structural Unit for Sequential Carbon–Carbon Bond Formation

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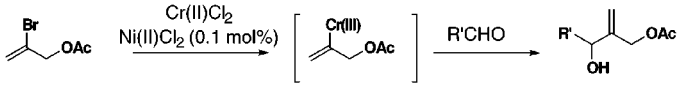
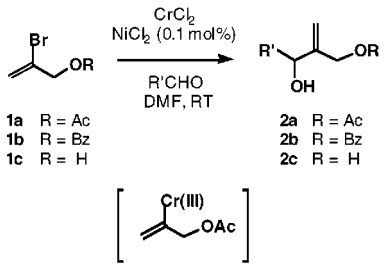
ABSTRACT



2-Bromoallyl acetate has been shown to be an efficient substrate for Ni(II)/Cr(II)-mediated coupling reactions with a variety of aliphatic and aryl aldehydes. Surprisingly, elimination of acetate from the intermediate vinylchromium species does not appear to compete with carbon–carbon bond formation. In addition, the allylic acetate products have been shown to be useful allyl nucleophile precursors through palladium-mediated reactions. These results suggest that acyloxyalkenyl bromides are efficient linchpins for multiple carbon–carbon bond formation.

The generation of organochromium compounds and their subsequent addition to aldehydes (Nozaki−Hiyama−Kishi reaction)[1] has become a powerful synthetic method. The initial step in this process is believed to involve activation of the carbon−halogen bond by oxidative addition of either Ni(0) or Ni(I) followed by transmetalation to a vinylchromium species. It is this chromium intermediate that is believed to undergo carbon−carbon bond formation with aldehydes. While this reaction has been used in the synthesis of a diverse range of complex natural products, to the best of our knowledge, there have been no reported examples using alkenyl halide precursors with a potential nucleofuge β to the alkenylchromium intermediate.[2] As part of our recent synthetic efforts[3] toward the total synthesis of the myriaporone class of natural products, we encountered the opportunity to test such a process. Herein, we report the successful utilization of β-acyloxyhalides in the Ni(II)/Cr(II) mediated coupling with aldehydes, Scheme 1. In addition, the allyl acetate products react efficiently in palladium-mediated reactions with aldehydes leading to diols utilizing remote 1,4 stereocontrol. Therefore, these acyloxyalkenyl bromides appear to be ideal linchpins for sequential carbon−carbon bond forming reactions.

Scheme 1



The reactions were carried out under the classic conditions previously reported by Kishi [0.1% Ni(II)/Cr(II) (3 equiv), vinyl bromide (2.5 equiv), aldehyde (1 equiv)] in dimethylformamide, room temperature for 8 h. An ethylenediamine workup is essential for reproducibly high yields of the allylic

(1) (a) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048−6050. (b) Jin, H.; Uenishi, J.-I.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644−5646.

(2) Nozaki has previously reported a successful allylic coupling of 1-bromo-2-chloro-2-propene with aldehydes under Cr(II) conditions.[1a] More recently, Wender and co-workers reported the successful generation of a number of heteroatom-substituted allylchromium reagents that were efficiently coupled with aldehydes without competitive elimination. Wender, P. A.; Wisniewski Grissom, J.; Hoffman, U.; Mah, R. *Tetrahedron Lett.* **1990**, *31*, 6605−6608.

(3) Taylor, R. E.; Ciavarri, J. P.; Hearn, B. R. *Tetrahedron Lett.* **1998**, *39*, 9361−9364.

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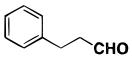
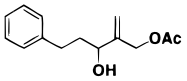
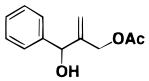
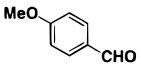
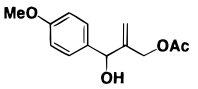
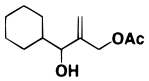
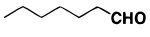
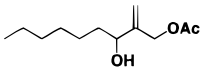
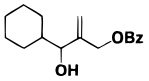
Table 1. Coupling Reactions between Vinyl Halides and Aldehydes

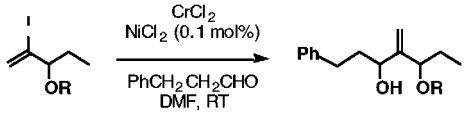
Entry	Vinyl halide	Aldehyde	Product	Yield
1	**1a**			93%
2	**1a**			54%
3	**1a**			40%
4	**1a**			86%
5	**1a**			74%
6	**1b**			77%

alcohol products.[4] As can be seen from Table 1, 2-bromoallyl acetate **1a** reacts efficiently with a variety of aromatic and aliphatic aldehydes to afford the resulting allylic alcohols in good yield, typically on the order of 80−90%. Coupling to aromatic aldehydes tended to produce lower yields of the desired product presumably due to the decreased stability of these products under the reaction conditions. Elimination does not appear to compete with the aldehyde coupling pathway, although products arising from elimination of acetate (allene) would not be isolable due to volatility. To quantify the potentially small degree of elimination that may be occurring, we chose to explore the related coupling reaction using 2-bromoallyl benzoate **1b** (entry 6). The coupling proceeded efficiently yielding the corresponding allylic alcohol in 77% yield. Unreacted vinyl bromide was easily recovered. Moreover, we were unable to detect any benzoic acid, a product of elimination, under careful analysis of the crude reaction mixture.

In an attempt to induce stereoselectivity in the newly formed chiral center, we have explored coupling reactions with substrates containing an allylic stereogenic center. Much to our surprise, vinyl iodide **3a** did not react even under forcing conditions, Scheme 2. In contrast, allylic ether **3b** did react with hydrocinnamaldehyde to provide the product diol **4b,** albeit in low (15−20%) yield. Moreover, the unprotected hydroxyl compound **3c** reacted to provide the allylic diol **4c** in >50% yield. In each case, the diastereoselectivity was modest at best, providing a 2:1 ratio of syn and anti stereoisomers. It appears that the reactivity of these substrates is subject to both the electronic and steric nature of the allylic functionality. To test the electronic effect of the acetoxy-protecting group, a competition study was carried out between allylic acetate **1a** and allylic alcohol **1c**. A 1:1 mixture of each vinyl halide was subjected to the coupling conditions with hydrocinnamaldehyde (0.5 equiv). The ratio of products (**2a**/**2c**) was greater than 10:1. Therefore, the lack of reactivity of protected substrates **3a** and **3b** relative to free hydroxyl **3c** must be attributed to steric effects.

We fully expect the allylic acyloxy products **2** to be ideal substrates for subsequent carbon−carbon bond formation particularly through Pd(0)-mediated reactions, Scheme 3.

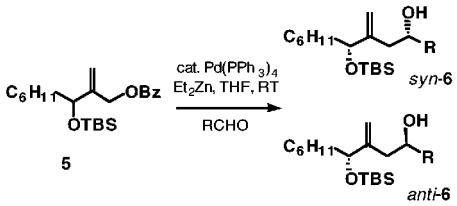
Scheme 2



3a R = Ac
3b R = CH_2OEt
3c R = H

4a R = Ac
4b R = CH_2OEt
4c R = H

Scheme 3



R	% Yield	*syn*	*anti*
Ph	83	75	25
C_6H_{11}-	61	75	25

Tamaru has recently developed conditions for the conversion of electrophilic π-allylpalladium species to allylic nucleophiles using diethylzinc.[5] The proposed mechanism involves a transmetalation step between the π-allylpalladium and diethylzinc to form an allylzinc species, the presumed active allylating agent.

In fact, exposure of allylic benzoate **5** to these conditions in the presence of either benzaldehyde or cyclohexanecarboxaldehyde efficiently provided alcohol **6** with fair 1,4 stereoinduction (75:25 syn/anti). Previous work from Mulzer[6] and Paquette[7] have shown selectivities that range from 5:1 to 99:1 for coupling reactions using similar allylic chromium and indium reagents generated from the corresponding allylic bromides.

The successful application of the Nozaki−Hiyama−Kishi coupling of 2-bromoallyl acetate to aldehydes represents a practical, ambient temperature alternative to allyl alcohol

(4) Stamos, D. P.; Sheng, X. C.; Chen, S. S.; Kishi, Y. *Tetrahedron Lett.* **1997**, *62*, 6355−6358.

(5) (a) Yasui, K., Goto, Y.; Yajima, T.; Taniseki, Y.; Fugami, K.; Tanaka, A.; Tamaru, Y. *Tetrahedron Lett.* **1993**, *34*, 7619−7622. (b) Tamaru, Y.; Tanaka, A.; Yasui, K., Goto, S.; Tanaka, S. *Angew. Chem., Int. Ed. Engl.* **1995**, *43*, 787−789. (c) Shimizu, M.; Kimura, M.; Tanaka, S.; Tamaru, Y. *Tetrahedron Lett.* **1998**, *39*, 609−612.

(6) Maguire, R. J.; Mulzer, J.; Bats, J. W. *J. Org. Chem.* **1996**, *61*, 6936−6940.

(7) Paquette, L. A.; Bennett, G. D.; Chhatriwalla, A.; Isaac, M. B. *J. Org. Chem.* **1997**, *62*, 3370−3374.

dianion[8] coupling reactions. A range of structural types of coupling partners have been successfully employed including aromatic and aliphatic aldehydes. Potential β-elimination in the organochromium intermediate does not appear to compete kinetically with carbon−carbon bond formation. In addition, the allylic acetate products have been shown to react efficiently in subsequent carbon−carbon bond-forming reactions. A search for reaction conditions that would allow both coupling events in a single step is currently underway. Application of this general methodology toward the synthesis of complex natural products will be reported in due course.

(8) Hegde, S. G.; Myles, D. C. *Synth. Commun*. **1997**, *27*, 2111−2115.

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Supporting Information Available: Detailed experimental as well as ^{1}H and ^{13}C NMR spectra for all new compounds is provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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