ORGANIC
LETTERS

2003
Vol. 5, No. 5
653−655

Regioselective Reductive Coupling of Alkynes and Aldehydes Leading to Allylic Alcohols

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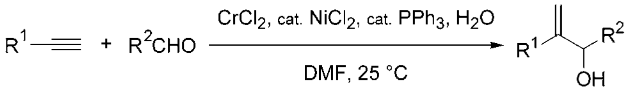
Received November 18, 2002

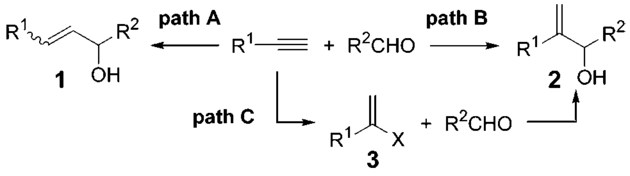
ABSTRACT



Treatment of a mixture of a terminal alkyne and an aldehyde with $CrCl_2$ and a catalytic amount of $NiCl_2$ and triphenylphosphine in the presence of water in DMF at 25 °C gives a 1,2-disubstituted allylic alcohol regioselectively.

Addition of a metal-hydride species to a terminal alkyne generates two regioisomeric alkenylmetal compounds, which afford the corresponding allylic alcohols upon treatment with an aldehyde. Because hydroboration, -alumination, and -zirconation of a terminal alkyne generate the corresponding (*E*)-alkenylmetal compound, the 3-alkyl-substituted allylic alcohol **1** is produced selectively via these hydrometalation methods (Scheme 1, path A).[1,2] Recent reports on intermolecular coupling reactions promoted with Et_3B and a catalytic amount of nickel also produce the alcohol **1** regioselectively.[3]

Scheme 1



In contrast, it is not easy to prepare the 2-alkyl-substituted allylic alcohol **2** directly from a terminal alkyne and an aldehyde (path B). Therefore, a two-step procedure via the 2-halo-1-alkene **3**[4] usually has been employed (path C).[5] We report herein a direct method for the preparation of the 2-substituted allylic alcohol **2** from a terminal alkyne and an aldehyde using chromium(II) under nickel catalysis.

Nucleophilic carbon−carbon bond formation with organometallic compounds, except organoboron and -indium reagents, is usually conducted under water-free conditions. Indeed, organochromium compounds hydrolyze with a lot of water.[6] On the other hand, the rate of hydrolysis is not so fast among the early transition metal compounds.[6c] Thus, the addition of an organochromium reagent can be accomplished without protecting the hydroxyl group of the substrate aldehyde in some cases,[7] and even a nucleophilic organochromium species can be generated by addition of a small aliquot of water.[8] Water is a typical proton source,

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[1] For representative examples using hydrozirconation, see: (a) Maeta, H.; Hashimoto, T.; Hasegawa, T.; Suzuki, K. *Tetrahedron Lett.* **1992**, *33*, 5965. (b) Wipf, P.; Xu, W. *Tetrahedron Lett.* **1994**, *35*, 5197.

[2] The reactivity of the alkenylboron and -aluminum species toward carbonyl compounds is low even when they are converted to the corresponding ate complexes. Thus, the alkenylboron and -aluminum species are usually converted to the corresponding halides with electrophilic sources of halides (iodine or *N*-bromosuccinimide), and metalated. (a) Brown, H. C.; Bowman, D. H.; Misumi, S.; Unni, M. K. *J. Am. Chem. Soc.* **1967**, *89*, 4531. (b) Zweifel, G.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 2753.

[3] (a) Oblinger, E.; Montgomery, J. *J. Am. Chem. Soc.* **1997**, *119*, 9065. (b) Huang, W.-S.; Chan, J.; Jamison, T. F. *Org. Lett.* **2000**, *2*, 4221.

[4] Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* **1990**, 675. See also: Takai, K.; Sakogawa, K.; Kataoka, Y.; Oshima, K.; Utimoto, K. *Org. Synth.* **1995**, *72*, 180.

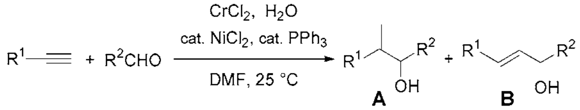
[5] For representative examples, see: Rowley, M.; Tsukamoto, M.; Kishi, Y. *J. Am. Chem. Soc.* **1989**, *111*, 2735. MacMillan, D. W. C.; Overman, L. E. *J. Am. Chem. Soc.* **1995**, *117*, 10391. Taylor, R. E.; Chen, Y. *Org. Lett.* **2001**, *3*, 2221.

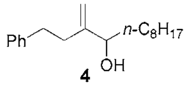
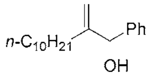
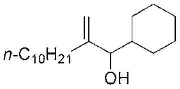
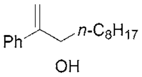
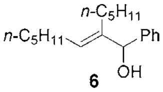
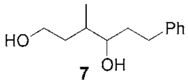
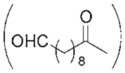
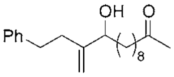
[6] Hanson, J. R.; Premuzic, E. *Angew. Chem., Int. Ed. Engl.* **1968**, *7*, 247. (b) Espenson, J. H. *Acc. Chem. Res.* **1992**, *25*, 222. (c) Wessjohann, L. A. *Synthesis* **1999**, 1.

[7] Kauffmann, T.; Abeln, R.; Wingbermühle, D. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 729.

10.1021/ol0272996 CCC: $25.00

Table 1. Coupling Reactions between Terminal Alkynes and Aldehydes[a]



entry	R^1	R^2	time (h)	major product	yield (%)	**A** / **B**
1	$Ph(CH_2)_2$	n-C_8H_{17}	8	 **4**	82	95 / 5
2			8		99^b	95 / 5
3	n-$C_{10}H_{21}$	Ph	8		80^b	94 / 6
4	n-$C_{10}H_{21}$	c-C_6H_{11}	8		79	90 / 10
5	Ph	n-C_8H_{17}	8		74	55 / 45
6	(6-dodecyne)	Ph	24	 **6**	$60^{b,c}$	–
7	$HO(CH_2)_2$	$Ph(CH_2)_2$	8	 **7**	83^d	>99 : <1
8	$Ph(CH_2)_2$		8		81	95 / 5

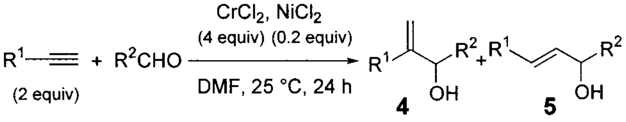
[a] Reaction was conducted on a 1.0-mmol scale. See typical procedure. [b] 3 mol of an alkyne, 6 mol of $CrCl_2$, 0.3 mol of $NiCl_2$, 0.6 mol of PPh_3, and 6 mol of water were used per mole of aldehyde. [c] $E/Z = 98/2$. [d] 3 mol of water was used per mole of aldehyde.

but in some cases it acts formally as a hydride anion or a hydrogen radical source by reaction with low-valent metals.[9] Therefore, we examined the addition of a small amount of water to a mixture of an alkyne, chromium(II) chloride, and a catalytic amount of nickel(II) chloride in the presence of an aldehyde to generate an alkenylchromium species[10] by formal hydrochromation of an alkyne.

To a stirred solution of chromium(II) chloride (4 equiv) and a catalytic amount of nickel(II) chloride (0.2 equiv) in DMF was added a solution of 4-phenyl-1-butyne (2 equiv) and nonanal (1 equiv) at 25 °C. A 1 M solution of water (2 equiv) in DMF was added slowly to the mixture at 25 °C, and the mixture was stirred at the same temperature for 6 h. Most of the alkyne and the aldehyde were recovered; however, the two desired allylic alcohols, 2-(2-phenylethyl)-1-undecen-3-ol (**4**) and (*E*)-1-phenyl-3-tridecen-5-ol (**5**), were detected after hydrolysis, though the combined yield was less than 3%. During the reaction, a deposition of nickel(0) was observed. Therefore, phosphine ligands were added to the mixture to prevent this deposition. Among those examined, triphenylphosphine was found to accelerate the reaction markedly.[11] In addition, the yield was improved by slow addition of a mixture of the alkyne and water to a mixture of the aldehyde, chromium(II) chloride, nickel(II) chloride, and triphenylphosphine in DMF. For example, when a mixture of 4-phenyl-1-butyne (2 equiv) and water (2 equiv) in DMF was added at 25 °C over a period of 2 h to a mixture of nonanal (1 equiv), chromium(II) chloride (4 equiv), nickel(II) chloride (0.2 equiv), and triphenylphosphine (0.4 equiv) in DMF, a mixture of the two allylic alcohols was obtained in 78% yield (**4**/**5** = 91/9, Scheme 2). The 2-alkyl-substituted allylic alcohol **4** was produced selectively. Although the addition of water to the mixture was indispensable for the reaction, the yield of allylic alcohols decreased when an excess amount (16 equiv) of water was added.

The results obtained with several kinds of alkynes and aldehydes are summarized in Table 1. Cyclotrimerization of

Scheme 2



$R^1 = Ph(CH_2)_2$
$R^2 = n$-C_8H_{17}

additive	**4**	**5**
H_2O	trace	trace
H_2O, PPh_3 (slow addition of the alkyne and H_2O)	71%	7%

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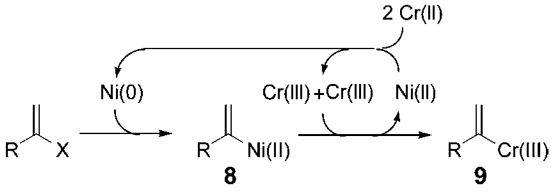
(8) Takai, K.; Toratsu, C. *J. Org. Chem.* **1998**, *63*, 6450. See also a review on water-accelerated organic transformations: Ribe, S.; Wipf, P. *Chem. Commun.* **2001**, 299.

(9) (a) Tolman, C. A. *J. Am. Chem. Soc.* **1970**, *92*, 6777. (b) Trost, B. M. *Chem. Eur. J.* **1998**, 2405.

(10) (a) Takai, K.; Tagashira, M.; Kuroda, T.; Oshima, K.; Utimoto, K.; Nozaki, H. *J. Am. Chem. Soc.* **1986**, *108*, 6048. (b) Jin, H.; Uenishi, J.-i.; Christ, W. J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 5644. (c) Hodgson, D. M.; Wells, C. *Tetrahedron Lett.* **1994**, *35*, 1601.

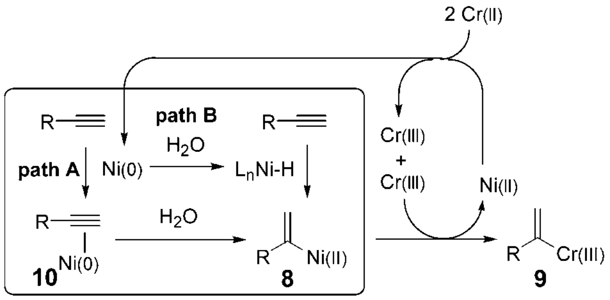
Scheme 3



the alkynes was observed as a side reaction, thus, 2−3 equiv of the alkyne was employed to obtain good yields. 2-Substituted allylic alcohols were obtained in a selective manner except in the case of phenyl acetylene (entry 5). An internal alkyne, 6-dodecyne, also reacted with an aldehyde to give the corresponding allylic alcohols in 60% yield though the reaction proceeded slowly (entry 6). The alcohol **6** was produced almost exclusively, and the stereochemistry of the double bond of **6** proved to be the *E* configuration. Since the coupling reaction is insensitive to a proton source, carbon−carbon bond formation could be accomplished without protecting the hydroxyl group (entry 7). In this case, one regioisomer **7** was produced exclusively, probably due to the coordination of the hydroxyl group to the nickel. A typical feature of the nucleophilic addition of organochromium reagents is their selective addition to aldehydes prior to ketone carbonyl groups.[6c,12] This was also observed in the reaction with a keto aldehyde (entry 8).

Similar to the reported alkenylchromium reagents (Scheme 3),[10] we assume that the alkenylchromium reagent **9** reported here is generated by transmetalation from the alkenylnickel species **8**.

Scheme 4



There are two possibilities for the formation of the alkenylnickel species **8** from terminal alkynes (Scheme 4). In path A, a terminal alkyne coordinates to nickel(0) generated by the reduction of nickel(II) with 2 equiv of chromium(II), and a nickel-alkyne complex **10** is produced. A reaction of the complex **10** with water gives the alkenylnickel species **8**,[13] which transmetalates to yield the alkenylchromium reagent **9**. In path B, nickel(0) reacts immediately with water to give a nickel-hydride species.[9] Addition of the nickel-hydride species to the terminal alkyne gives the alkenylnickel species **8**.[9a]

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas from the Ministry of Education, Culture, Sports, Science and Technology of Japan and by the Nagase Science and Technology Foundation.

Supporting Information Available: General experimental procedure and characterization data for all compounds in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

OL0272996

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[11] Effects of additives on the yields and regioselectivities of the reactions between 4-phenyl-1-butyne and nonanal are as follows: PBu_3, 14% (**4**/**5** = 0/100); P(*o*-tolyl)$_3$, 16% (64/36); P(2-franyl)$_3$, 18% (78/22); P[3,5-$(CF_3)_2C_6H_3$]$_3$, 30% (90/10); P[2,6-$(MeO)_2C_6H_3$]$_3$, <5%.

[12] Takai, K.; Utimoto, K. *J. Synth. Org. Chem., Jpn.* **1988**, *46*, 66. Fürstner, A. *Chem. Rev.* **1999**, *99*, 991.

[13] Bennett, M. A.; Castro, J.; Edwards, A. J.; Kopp, M. R.; Wenger, E.; Willis, A. C. *Organometallics* **2001**, *20*, 980.