ORGANIC LETTERS

2005
Vol. 7, No. 14
2957−2960

Stereoselective 4-Benzyloxybut-2-enylation of Aldehydes via an Allyl-Transfer Reaction Using a Chiral Allyl Donor

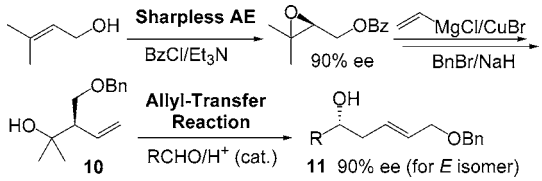
Siddiqi M. Shafi, Jingyu Chou, Kazuhide Kataoka, and Junzo Nokami*

Department of Applied Chemistry, Okayama University of Science, 1-1 Ridai-cho, Okayama 700-0005, Japan

nogami@dac.ous.ac.jp

Received April 22, 2005

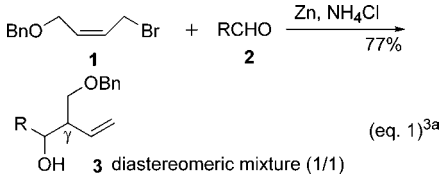
ABSTRACT



A direct and highly stereoselective (*E*)-4-benzyloxybut-2-enylation of aldehydes was successfully carried out to give 5-benzyloxyhomoallylic alcohol (11) via an allyl-transfer reaction using a chiral allyl donor (10). The chiral allyl donor (10) was prepared by catalytic Sharpless asymmetric epoxidation of 3-methylbut-2-en-1-ol, followed by a stereospecific vinyl Grignard reaction of the epoxide in the presence of CuBr and selective benzylation of the primary alcohol of diol.

The reaction of an allylic nucleophile with an aldehyde (or ketone) is one of the most attractive and practical carbon−carbon bond formation reactions to give a homoallylic alcohol. In this reaction, the product has both a chiral center and a double bond, which serve as useful building blocks in organic synthesis.[1] There are many reports on the preparation of highly optically active homoallyl(ic) alcohols, including substituted homoallyl alcohols, via nucleophilic allylation of an aldehyde using allyl(ic)metal reagents.[2]

However, there are few reports on the reaction of aldehydes with 4-alkoxyalk-2-enylmetallic compounds. One exception is the Barbier-type reaction of an aldehyde with 1-bromo-4-benzyloxybut-2-ene **1** and zinc (under Luche's condition), in which the corresponding γ-adduct of the homoallylic alcohol is obtained regioselectively with low diastereoselectivity, although the corresponding allylic zinc compound is not detected (eq 1).[3a]

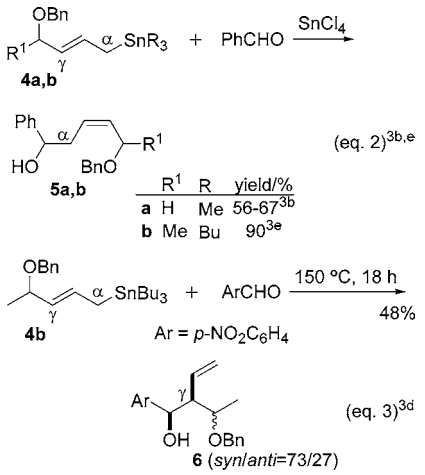


Another exception is the reaction of (4-alkoxyalk-2-enyl)-trialkylstannanes **4** with an aldehyde in the presence or absence of tin(IV) chloride to give the corresponding α-adduct **5** or γ-adduct **6** of the homoallylic alcohol (eqs 2 and 3) which is reported by Naruta[3b] and Thomas[3c,d] independently.

It is reasonable to expect that an elimination reaction will take place by treatment of a 4-alkoxyalk-2-enyl halide with metal, such as Mg and Zn, to give a diene. Therefore, the

(1) For reviews on reactions using allyl(ic) metals, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Marshall, J. A. In *Lewis Acids in Organic Synthesis*; Yamamoto, H., Ed.; Wiley-VCH: New York. 2000; Vol. 1. For reviews on asymmetric allylations and related reactions, see: (c) Denmark, S. E.; Almstead, N. G. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: New York, 2000. (d) Chemler, S. R.; Roush, W. R. In *Modern Carbonyl Chemistry*; Otera, J., Ed.; Wiley-VCH: New York, 2000.

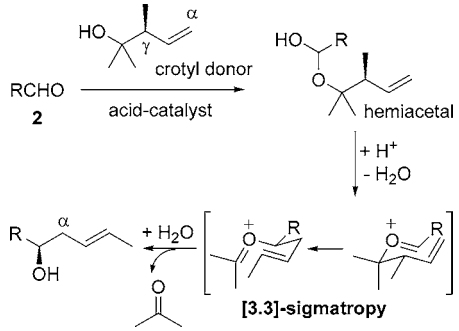
10.1021/ol050890t CCC: $30.25
Published on Web 06/08/2005



reaction does not give an allylic metal compound that is stable enough to react with an aldehyde stereoselectively to give the corresponding homoallylic alcohol, although (4-alkoxyalk-2-enyl)trialkylstannanes **4** are stable enough as a result of the high covalent character of the R_3Sn-C (R = alkyl) bond as shown above (eqs 2 and 3).

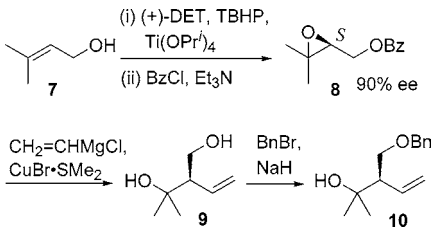
These facts prompted us to establish a convenient method for enantioselective 4-benzyloxybut-2-enylation of an aldehyde via an allyl-transfer reaction.[4] In the reaction, the alk-2-enylation of the aldehyde is not a nucleophilic reaction. Rather, it is a [3.3]-sigmatropic rearrangement, in which C−C bond formation and cleavage take place concertedly via a six-membered transition state. That is, direct but-2-enylation of aldehydes **2** will take place to give the corresponding α-adduct of homoallylic alcohols via allyl-transfer reaction using a stable and environmentally friendly crotyl donor, such as 2,3-dimethylpent-4-en-2-ol, in the presence of an acid catalyst as shown in Scheme 1.

Scheme 1. But-2-enylation of Aldehyde via Allyl-Transfer Reaction



Therefore, we attempted to prepare a new chiral 4-benzyloxybut-2-enyl donor **10** via a highly stereoselective reaction of vinylmagnesium chloride with the optically active epoxide **8** formed by Sharpless AE (asymmetric epoxidation) of 3-methylbut-2-enol **7**, as shown in Scheme 2.

Scheme 2. Preparation of Chiral 4-Benzyloxybut-2-enyl Donor **10**



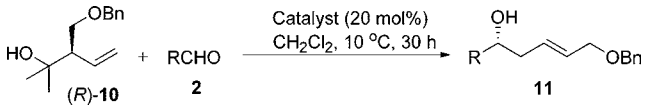
The Sharpless AE reaction of 3-methylbut-2-en-1-ol **7**, using *tert*-butylhydroperoxide (TBHP) with 12 mol % of (+)-diethyl tartrate and titanium(IV) isopropoxide, followed by benzoylation, gave **8** in 70% yield with >90% ee.[5] To a solution of **8** (2 mmol), dimethyl sulfide (0.6 mL), and $CuBr\cdot SMe_2$ (3.2 mmol) in ether (4 mL) was added vinylmagnesium chloride (8 mL; 1 M THF solution) at −25 °C, and the reaction mixture was stirred for 5 h at −25 °C and then stirred overnight at room temperature under an argon atmosphere.[6] While protecting the hydroxyl group of the diol, **9** was converted to the corresponding benzyl ether **10** by treatment with sodium hydride and benzyl bromide in THF.

(2) Asymmetric alk-2-enylation of aldehydes; for a review, see: (a) Denmark, S. E.; Fu, J. *Chem. Rev.* **2003**, *103*, 2763. Original papers, for example: catalytic asymmetric allylation with chiral catalyst, by allylsilanes: (b) Wadamoto, M.; Ozasa, N.; Yanagisawa, A.; Yamamoto, H. *J. Org. Chem.* **2003**, 68, 5593 and references therein. (c) Malkov, A. V.; Orsini, M.; Pernazza, D.; Muir, K. W.; Langer, V.; Meghani, P.; Kocovsky, P. *Org. Lett.* **2002**, 4, 1047. (d) Malkov, A. V.; Dufková, L.; Farrugia, L.; Kocovsky, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 3674. By allylboronate: (e) Wada, R.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2004**, *126*, 8910. Asymmetric allylation with stoichiometric chiral auxiliary, by allylboronate: (f) Lachance, H.; Lu, X.; Gravel, M.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 10160. (g) Rauniyar, V.; Hall, D. G. *J. Am. Chem. Soc.* **2004**, *126*, 4518. By allylsilane: (h) Kubota, K.; Leighton, J. L. *Angew. Chem., Int. Ed.* **2003**, *42*, 946.

(3) Barbier reactions of aldehydes (RCHO) with zinc dust and (*Z*)-4-benzyloxy-1-bromobut-2-ene ($BnOCH_2CH{=}CHCH_2Br$) under Luche's condition to give the corresponding homoallylic alcohol γ-adducts [$RCH(OH)CH(CH_2OBn)CH{=}CH_2$] in low de: (a) Chattopadhyay, A.; Dhotare, B.; Hassarajani, S. *J. Org. Chem.* **1999**, *64*, 6874. 4-Alkoxyalk-2-enylstannanes (e.g., $BnOCH_2CH{=}CHCH_2SnMe_3$) were prepared by a coupling reaction of the corresponding bromide with Me_3SnLi and treated with benzaldehyde in the presence of $SnCl_4$ to give unusual adducts [(*Z*)-$PhCH(OH)CH_2CH{=}CHCH_2OBn$] highly selectively, regardless of the stereochemistry of allylstannane: (b) Naruta, Y.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1983**, 1264. 4-(*tert*-Butyldimethylsilyloxy)but-2-enylzirconium reagent ($TBDMSOCH_2CH{=}CHCH_2ZrCp_2OTBDMS$) was prepared via oxidative addition of "$ZrCp_2$" with 1,4-bis(*tert*-butyldimethylsilyloxy)-but-2-ene and was treated with aldehydes to give the corresponding γ-adducts anti selectively [$RCH(OH)CH(CH_2OTBDMS)CH{=}CH_2$]: (c) Clark, A. J.; Kasujee, I.; Peacock, J. L. *Tetrahedron Lett.* **1995**, *36*, 7137. 4-Benzyloxypent-2-enyltributylstannane was prepared from the corresponding dithiocarbonate [$CH_3CH(OBn)CH(SCOSCH_3)CH{=}CH_2$] with tributyltin hydride in the presence of AIBN: (d) Mortlock, S. V.; Thomas, E. J. *Tetrahedron Lett.* **1988**, *29*, 2479. Thomas et al. also discovered that the reaction of the allylicstannane with aldehydes in the presence of $SnCl_4$ gave (*Z*)-5-benzyloxyhomoallylic alcohols [(*Z*)-$RCH(OH)CH_2CH{=}CHCH(OBn)CH_3$] highly selectively: (e) McNeill, A. H.; Thomas, E. J. *Tetrahedron Lett.* **1990**, *31*, 6239; **1992**, *33*, 1369; *Synthesis* **1994**, 322.

(4) (a) Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S. *J. Am. Chem. Soc.* **1998**, *120*, 6609. (b) Sumida, S.; M. Ohga, M.; Mitani, J.; Nokami, J. *J. Am. Chem. Soc.* **2000**, *122*, 1310. (c) Nokami, J.; Anthony, L.; Sumida, S. *Chem. Eur. J.* **2000**, *6*, 2909. (d) Nokami, J.; Ohga, M.; Nakamoto, H.; Matsubara, T.; Hussain, I.; Kataoka, K. *J. Am. Chem. Soc.* **2001**, *123*, 9168. (e) Hussain, I.; Komasaka, T.; Ohga, M.; Nokami, J. *Synlett* **2002**, 640. (f) Nokami, J.; Nomiyama, K.; Matsuda, S.; Imai, N.; Kataoka, K. *Angew. Chem., Int. Ed.* **2003**, *42*, 1273. (g) Nokami, J.; Nomiyama, K.; Shafi, S.; Kataoka, K. *Org. Lett.* **2004**, *6*, 1261. (h) Nokami, J. *J. Synth. Org. Chem. Jpn.* **2003**, *61*, 992.

Table 1. Asymmetric 4-Benzyloxybut-2-enylation of Aldehydes via Allyl-Transfer Reaction by Chiral Allyl Donor **10**[a]



	RCHO **2**		(*R*)-**10**		product **11**			
entry		R	% ee[b]	catalyst[c]		yield (%)[d]	% ee[e]	*E*/*Z*[e]
1	**2a**	$Ph(CH_2)_2$	85	TfOH	(*S*)-**11a**	80	86	18/1
2	**2a**	$Ph(CH_2)_2$	90	TfOH	(*S*)-**11a**	82	90	21/1
3[f]	**2a**	$Ph(CH_2)_2$	85	TfOH	(*S*)-**11a**	80	85	12/1
4[f]	**2a**	$Ph(CH_2)_2$	90	TfOH	(*S*)-**11a**	80	90	11/1
5[f]	**2a**	$Ph(CH_2)_2$	85	$Sn(OTf)_2$	(*S*)-**11a**	75	86	35/1
6[f]	**2a**	$Ph(CH_2)_2$	85	*p*-TsOH·H_2O	(*S*)-**11a**	40	86	58/1
7[f]	**2a**	$Ph(CH_2)_2$	85	$SnCl_4$	(*S*)-**11a**	66	85	12/1
8[f,g]	**2a**	$Ph(CH_2)_2$	85	TfOH	(*S*)-**11a**	92	86	12/1
9[f,h]	**2a**	$Ph(CH_2)_2$	84	TfOH	(*R*)-**11a**	79	83	12/1
10	**2b**	$PhS(CH_2)_2$	90	TfOH	(*R*)-**11b**	76	90	10/1
11[f]	**2b**	$PhS(CH_2)_2$	90	TfOH	(*R*)-**11b**	82	90	10/1
12	**2c**	$BnO(CH_2)_5$	90	TfOH	(*S*)-**11c**	86	90	26/1
13	**2d**	$CH_3(CH_2)_4$	90	TfOH	(*S*)-**11d**	77	90	35/1
14[f]	**2d**	$CH_3(CH_2)_4$	90	TfOH	(*S*)-**11d**	77	90	21/1
15	**2e**	$CH_2{=}CH(CH_2)_7$	90	TfOH	(*S*)-**11e**	78	90	29/1
16[f]	**2e**	$CH_2{=}CH(CH_2)_7$	90	TfOH	(*S*)-**11e**	80	90	22/1
17	**2f**	$(CH_3)_3C$	90	TfOH	(*R*)-**11f**	60	90	20/1

[a] All reactions were performed with allyl donor (*R*)-**10** (0.5 mmol), aldehydes **2** (0.5 mmol), and TfOH (20 mol %) in CH_2Cl_2 (2.5 mL) at 10 °C for 30 h unless otherwise stated. [b] Determined by HPLC analysis (CHIRALCEL AD-H), using hexane/Pr^{i}OH (40/1) as eluent, flow rate 0.3 mL/min. [c] TfOH (trifluoromethnesulfonic acid); $Sn(OTf)_2$ (tintriflate); *p*-TsOH·H_2O (*p*-toluenesulfonic acid monohydrate). [d] Isolated yield of *E* and *Z* mixture. [e] % ee values of *E* and *E*/*Z* ratio were determined by HPLC analysis (CHIRALCEL AD-H) using hexane/PriOH (20/1) as eluent, flow rate 0.3 mL/min. [f] Performed at 20 °C for 20 h. [g] Performed with 2.0 equiv of (*R*)-**10** to aldehyde **2a**. [h] Performed with allyl donor (*S*)-**10** prepared via Sharpless AE using (−)-DET.

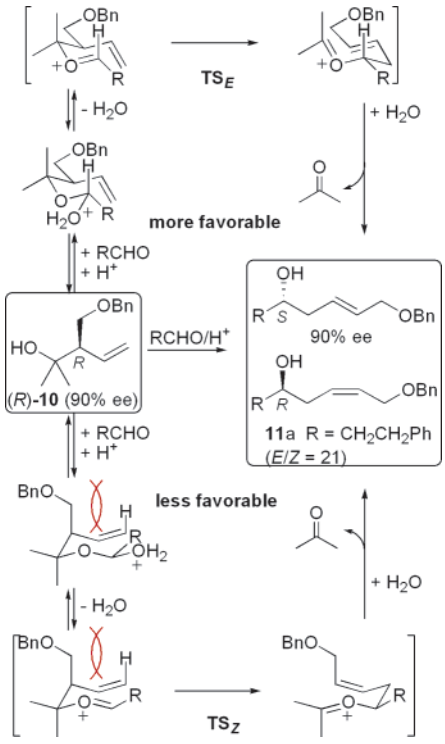
After stirring for 12 h at room temperature and the usual workup of the reaction mixture, pure **10** was obtained by column chromatography on silica gel. The optical purity was determined to be 90% ee by HPLC using CHIRALCEL AD-H (Daicel Co. Ltd.) with *n*-hexane/2-propanol (40/1).

4-Benzyloxybut-2-enylation of aldehydes via allyl-transfer reaction using the allyl donor **10** thus obtained was carried out in the presence of an acid catalyst to give the optically active (2*E*)-1-benzyloxyalk-2-en-5-ols **11** in good yields with high ee, which depended on that of the Sharpless AE (Table 1). Higher *E* selectivity was observed at 10 °C rather than 20 °C.

It is noteworthy that tin tetrachloride ($SnCl_4$) served as a catalyst similar to trifluoromethansulfonic acid (TfOH) and gave **11a** from **10** in the same enantioselectivity (85% ee) and *E*/*Z* selectivity (12/1) (entries 3 and 7 in Table 1).

The stereoselectivities (enantio- and *E*/*Z* selectivity) of the product via this allyl-transfer reaction were dependent on both the optical purity of the allyl donor **10** and the conformational stability of the six-membered ring chairlike

Scheme 3. 4-Benzyloxybut-2-enylation of Aldehyde via Allyl-Transfer Reaction



(5) (a) Suga, T.; Ohta, S.; Ohmoto, T. *J. Chem. Soc., Perkin Trans. 1* **1987**, 2845. Higher ee (>95% ee) will be obtained via recrystalization of its *p*-nitrobenzoyl ester: (b) Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.

(6) Highly stereoselective copper(I)-catalyzed C−C bond formation of *β*,*γ*-epoxy alcohols with Grignard reagents: (a) Tius, M. A.; Fauq, A. H. *J. Org. Chem.* **1983**, *48*, 4131. (b) Roush, W. R.; Adam, M. A.; Walts, A. E. Harris, D. J. *J. Am. Chem. Soc.* **1986**, *108*, 3422. (c) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 6339.

transition state (**TS**) formed from **10** and aldehydes. This means that the proposed 4-benzyloxybut-2-enylation also takes place in a stereospecific manner via a conformationally more stable six-membered chairlike transition state $\mathbf{TS}_E$ from optically active γ-adducts of homoallylic alcohols **10** as well as crotylation (Scheme 3).[2] That is, any remarkable effect of the benzyloxy group was observed in the stereochemistry of the allyl-transfer reaction, even if it was catalyzed by tin tetrachloride.

The configuration of the *Z* isomer was determined to be opposite of that of the major product (*E* isomer) as follows: hydrogenation of the allyl-transfer product (*S*)-**11a** (86% ee, $E/Z = 18/1$, entry 1 in Table 1) gave 7-benzyloxy-1-phenylheptan-3-ol in 85% yield with 77% ee, showing that the configuration of the major Z isomer of **11a** should be *R*. The amount of the minor *Z* isomer of **11a** was too small for it to be detected by HPLC analysis.

Selective deprotection of the benzyl group of **11** was easily carried out by treatment with powdered Ca in liquid NH_3.[7]

In conclusion, we propose a flexible, environmentally friendly, and *E*-selective 4-benzyloxybut-2-enylation of aldehydes via an allyl-transfer reaction. In this reaction, we can obtain the desired enantiomer selectively by a choice of (+)- or (−)-diethyltartrate in the Sharpless AE reaction of 3-methylbut-2-en-1-ol in the preparation of the allyl donor (**10**).

Acknowledgment. This work was financially supported by a Grant in Aid for Scientific Research from the Ministry of Education, Science, Culture, and Sports, Japan (no. 15350063), the Okayama Science and Technology Foundation, and a Grant for Cooperative Research Administered by the Japan Private School Promotion Foundation.

Supporting Information Available: Experimental procedures and complete characterization (^{1}H and ^{13}C NMR, IR, and elemental analysis or mass spectra) for compounds **10** and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL050890T

(7) (a) Hwu, J. R.; Chua, V.; Schroder, J. E.; Barrans, R. E., Jr.; Khoudary, K. P.; Wang, N.; Wetzel, J. M. *J. Org. Chem.* **1986**, *51*, 4731. (b) Hwu, J. R.; Wein, Y. S.; Leu, Y.-J. *J. Org. Chem.* **1996**, *61*, 1493.