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A New Protocol for the Acetoxyallylation of Aldehydes Mediated by Indium in THF

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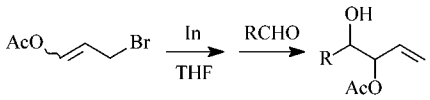
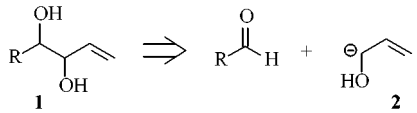
ABSTRACT



A new precursor of a formal 1-hydroxy allyl anion is represented by 3-bromo-1-acetoxy-1-propene, which is synthesized by the $ZnCl_2$-catalyzed addition of acetyl bromide to propenal. 3-Bromo-1-acetoxy-1-propene reacts with indium powder in THF to give the corresponding 3-acetoxylated ally indium complex, which regioselectively adds to aldehydes, affording monoprotected 1-en-3,4-diols. Diastereoselectivity mainly depends on the nature of the aldehyde; saturated aldehydes afford *anti* adducts, whereas the α,β-unsaturated aldehydes preferentially lead to the *syn* isomers.

Syn and *anti* 1-en-3,4-diols **1** are attractive building blocks in connection with the total synthesis of a variety of polyoxy natural products. Double bond epoxidation, dihydroxylation, ozonization, etc. open routes to epoxydiols, tetrols, dihydroxyaldehydes, etc. Much effort has been devoted for the past two decades to the development of synthetic equivalents of 1-hydroxy allyl anion **2**, as direct and ideal candidates for the synthesis of **1** via regioselective addition to aldehydes (Scheme 1).[1]

Scheme 1



1 **2**

The most straightforward but less studied synthetic equivalent of **2** is represented by **2a**, reported by Still and Evans in the 1970s[2] and recently exploited by us (R = TBS) in a totally *anti* selective addition to a nitrone.[3]

2a

A selection of further 3-substituted allylic organometallic reagents mimicking **2** is reported in Figure 1.

Synthetic equivalents of **2** are divided into two goups depending on the simple diastereoselectivity obtained in the addition to aldehydes. Moreover, we distinguish between η^1 organometallic compounds **2b**,[4] **2c**,[5] **2d**,[6] **2e**,[7] **2f**,[8] **2g**,[9] **2h**,[10] **2i**,[11] **2j**,[12] **2k**,[13] and **2l**[14] carrying an alkoxy or silyloxy group, and borylated or silylated allyl organometallic reagents **2m**,[15]

(1) Katritzky, A. R.; Piffl, M.; Lang, H.; Anders, E. *Chem. Rev.* **1999**, *99*, 665.
(2) (a) Evans, D. A.; Andrews, G. C.; Buckwalter, B. *J. Am. Chem. Soc.* **1974**, *96*, 5560. (b) Still, W. C.; Macdonald, T. L. *J. Am. Chem. Soc.* **1974**, *96*, 5561. (c) Still, W. C.; Macdonald, T. L. *J. Org. Chem.* **1976**, *41*, 3620.
(3) Lombardo, M.; Spada, S.; Trombini, C. *Eur. J. Org. Chem.* **1998**, 2361.
(4) Hoffmann, R. W.; Metternich, R.; Lanz, J. W. *Liebigs Ann. Chem.* **1987**, 881. See also: Hoffmann, R. W.; Kemper, B. *Tetrahedron Lett.* **1981**, *22*, 5263.
(5) Ganesh, P.; Nicholas, K. M. *J. Org. Chem.* **1997**, *62*, 1737.
(6) Hirashita, T.; Kamei, T.; Horie, T.; Yamamura, H.; Kaway, M.; Araki, S. *J. Org. Chem.* **1999**, *64*, 172.
(7) Keck, G. E.; Abbott, D. E.; Wiley: M. R. *Tetrahedron Lett.* **1987**, *28*, 139.
(8) Roush, W. R.; VanNieuwenhze, M. S. *J. Am. Chem. Soc.* **1994**, *116*, 8536.
(9) (a) Micalizio, G. C.; Pinchuk, A. N.; Roush, W. R. *J. Org. Chem.* **2000**, *65*, 8730. (b) Micalizio, G. C.; Roush, W. R. *Tetrahedron Lett.* **1999**, *40*, 3351. (c) Watrelot-Bourdeau, S.; Parrain J.-L.; Quintard, J.-P. *J. Org. Chem.* **1997**, *62*, 8261.
(10) Yamamoto, Y.; Komatsu, T.; Maruyama, K. *J. Organomet. Chem.* **1985**, *285*, 31.
(11) Chika, J.-I.; Takei, H. *Tetrahedron Lett.* **1998**, *39*, 605.

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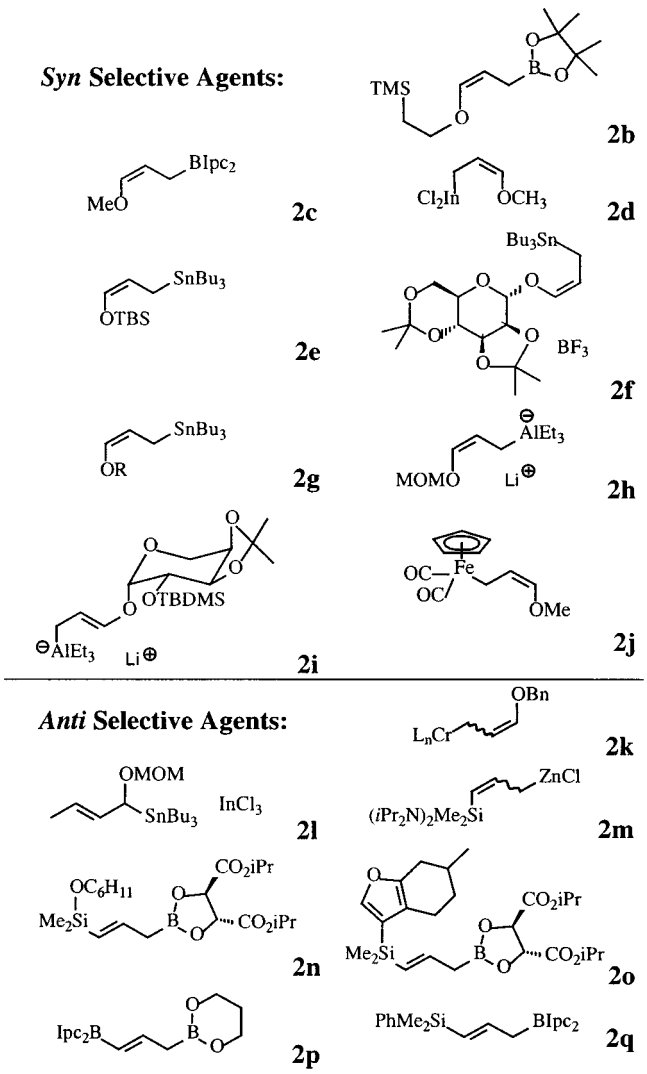


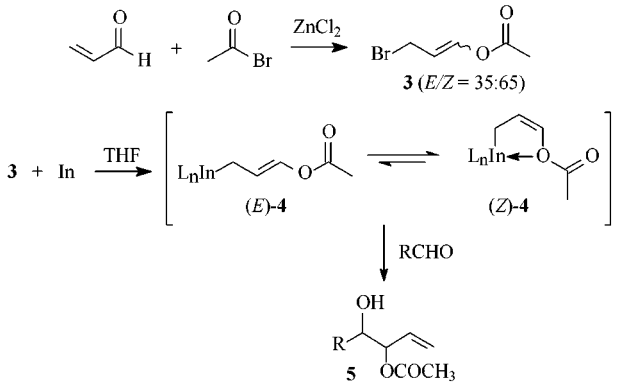
Figure 1. Examples of 3-heterosubstituted allyl organometallic compounds.

2n,[16] **2o**,[17] **2p**,[18] and **2q**[19] where silicon and boron act as masked forms of a hydroxy group.

The preparation of organometallic derivatives **2** generally requires metalation of a precursor with alkyllithium bases, followed by transmetalation to give the desired intermediate. The use of organolithium compounds limits the choice of the RO substituent on the allylic moiety to base-tolerant groups.

While searching for a new synthetic equivalent of **2** easily accessible from simple starting materials, we perceived a solution in a neglected reaction, namely, the 1,4-haloacylation of acrolein.[20] Use of acetyl bromide allowed us to synthesize 1-acetoxy-3-bromo-1-propene (**3**) in multigram scale as a 35:65 mixture of *E*/*Z* isomers. Upon exposure of **3** to indium powder in THF, 3-acetoxy allyl indium species **4** are readily formed and may be successively trapped by aldehydes [21] to give 1-en-3-acetoxy-4-ols **5** in high yield (Scheme 2).

Scheme 2



The overall stepwise protocol is simple and highly reproducible. Table 1 collects preliminary results in addition reactions of **4** to prochiral aldehydes in THF using indium powder.[22]

Table 1. Stepwise Synthesis of **6** in THF

entry	RCHO	t_1 (h)[a]	T_1 (°C)[a]	T_2 (°C)[b]	**6** (**Y**, %)	*syn*/*anti*
1	PhCHO	4	25	25	**6a** (86)	70/30
2	PhCHO	4	0 → 25	−50	**6a** (89)	85/15
3	PhCHO	4	0 → 25	−78	**6a** (91)	85/15
4	PhCHO	12	0 → 25	0	**6a** (82)	70/30
5	PhCHO	0	25	25	**6a** (74)	60/40
6	PhCHO (Mn/In)[c]	0	25	25	**6a** (60)	60/40
7	$C_6H_{11}CHO$	4	0 → 25	0	**6b** (81)	15/85
8	$C_6H_{11}CHO$	4	−20	−20	**6b** (96)	15/85
9	$C_6H_{11}CHO$	4	0 → 25	−78	**6b** (70)	10/90
10	$C_6H_{11}CHO$	0	0 → 25	0	**6b** (70)	25/75
11	n-$C_{10}H_{21}CHO$	4	0	0	**6c** (75)	35/65
12	$(CH_3)_2CHCH_2CHO$	4	0 → 25	0	**6d** (82)	35/65
13	$PhCH_2CH_2CHO$	4	0 → 25	0	**6e** (95)	30/70
14	(*E*)-PhCH=CHCHO	4	0 → 25	0	**6f** (96)	70/30
15	CH_2=(CH_3)CHCHO	4	0 → 25	0	**6g** (79)	85/15
16	2-furyl-CHO	4	0 → 25	−78	**6h** (72)	90/10

[a] t_1 and T_1 refer to time and temperature required for the formation of **4**. [b] The reaction of **4** with the aldehyde is carried out for 4 h at T_2. [c] The following molar ratios were used: In (0.1 equiv), Mn (2 equiv), **3** (1.5 equiv), TMSCl (1.1 equiv), and PhCHO (1 equiv).

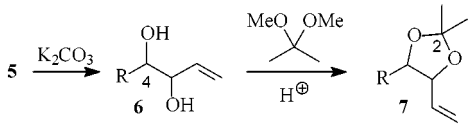
Barbier-type protocols were also tested, consisting of the contemporary addition of **3** and the aldehyde to indium in THF with stirring at room temperature (entries 5, 6, and 10). Under Barbier conditions, the reaction can be made catalytic in indium by using manganese as reducing stoichiometric metal (entry 6), thus reducing the cost of the reaction, even though a lower yield is obtained.[23]

To evaluate the stereochemical outcome of the reaction, the crude product mixture is hydrolyzed with K_2CO_3/CH_3-

(12) Jiang, S.; Agoston, G. E.; Chen, T.; Cabal, M. P.; Turos, E. *Organometallics* **1995**, *14*, 4697.
(13) Takai, K.; Nitta, K.; Utimoto, K. *Tetrahedron Lett.* **1988**, *29*, 5263.
(14) Marshall, J. A.; Hinkle, K. W. *J. Org. Chem.* **1995**, *60*, 1920.
(15) Tamao, K.; Nakajo, E.; Ito, Y. *J. Org. Chem.* **1987**, *52*, 957.
(16) Roush, W. R.; Grover, P. T.; Lin, X. *Tetrahedron Lett.* **1990**, *31*, 7563.
(17) Hunt, J. A.; Roush, W. R. *Tetrahedron Lett.* **1995**, *36*, 501.
(18) Brown, H. C.; Narla, G. *J. Org. Chem.* **1995**, *60*, 4686.
(19) Micalizio, G. C.; Roush, W. R. *Org. Lett.* **2001**, *12*, 1949.

OH/H_2O to 1-en-3,4-diols **6** and then transformed into the corresponding 1,3-dioxolanes **7** (Scheme 3). *Syn/anti* assign-

Scheme 3



ments were attributed on the basis of the following observations: (i) The chemical shift of the homoallylic proton (H-4) in *syn*-**6** is always 0.1−0.3 ppm upfield from that of *anti*-**6**, as previously reported in the literature.[12] (ii) The difference of chemical shifts of the two methyl groups in position 2 is always greater in *cis*-**7** (0.12−0.14 ppm), coming from *anti*-**6**, than in *trans*-**7** (0.01−0.04 ppm). (iii) Invariably, GC retention times of *trans* dioxolanes **7** are shorter than those of *cis*-**7** (30-m column packed with HP-5 cross-linked 5% Me Ph Silicone; temperature ramping from 50 to 250 °C, at 10 °C/min).

In regards to simple diastereoselectivity, we observed that stereopreference in the addition to prochiral aldehydes mainly depends on the nature of the aldehyde. While conjugated aldehydes preferentially lead to *syn* adducts (entries 1−6, 14−16), saturated aldehydes favor the formation of *anti* adducts (entries 7−13). The γ-oxygenated allyl indium species most contiguous to **4**, namely, methoxylated (*Z*)-**2d**,[6] was reported to react with benzaldehyde, cinnamaldehyde and octanal, always favoring *syn* adducts, with the *syn*/*anti* ratios 87:13, 56:44, and 82:18, respectively. These results indicate that the γ-acetoxy group exerts different effects with respect to the γ-methoxy group.

Our standard protocol involves the preliminary formation of **4** before the addition of the aldehyde; during the time interval t_1 1,3-metallotropic shift of indium is supposed to take place, in our opinion favoring (*Z*)-**4**, thermodynamically stabilized by an indium−oxygen interaction, as occurs in **2d**.[6] Increasing t_1 (entry 4) does not improve diastereoselectivity, and better results are obtained by lowering the reaction temperature (entries 2, 4, 9, and 16).

On the other hand, if a classical Barbier procedure is adopted, that means $t_1 = 0$ h, diastereoselectivity is quite lower (entries 5 and 10). In these cases it is possible to assume that the *E*/*Z* isomeric mixture of **4** reflects that of starting **3** (*E*/*Z* = 35:65) and trapping by the aldehyde occurs before any enrichment takes place by 1,3-metallotropic shift.

A rationale for our observation is possible considering transition states (TS) **A**−**D**, where the more stable (*Z*)-**4** is assumed to react with its *re* face (Figure 2). Zimmermann-type chairlike TSs **C** and **D** are generally considered to account for the *syn* selectivity of *Z*-crotyl species.[21] By extending the same reasoning to (*Z*)-**4**, *syn* adducts should always prevail because of the lack in **D** of 1,3 diaxial destabilizing interactions. In our opinion boat (**A**) and twist-boat (**B**) shaped TSs are more stable than **C** and **D** since they preserve the attractive indium−oxygen interaction present in (*Z*)-**4**. In TS **A** leading to *anti*-**5**, the saturated aldehyde offers the *si* face in order to accommodate the R chain in the less encumbered position. In TS **B** the unsaturated aldehyde offers the *re* face, so enjoying $\pi-\pi$ stabilizing interaction between the acetyl group and the unsaturated substituent. Aromatic aldehydes and cinnamaldehyde exhibit the best stereopreference thanks to a more effective $\pi-\pi$ interaction.

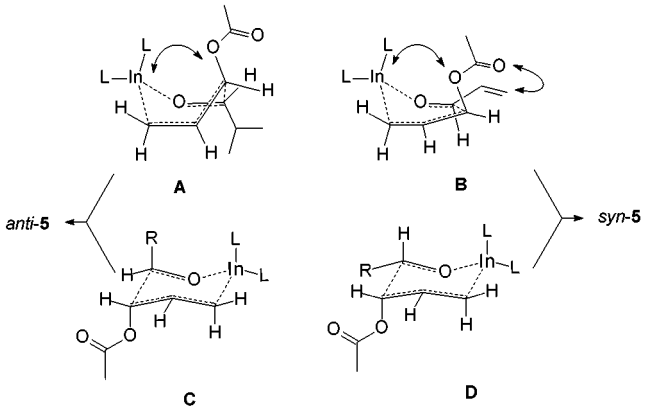


Figure 2. Possible TSs for the addition of (*Z*)-**4** to aldehydes.

In conclusion, summarizing the advantages of this route to 1-en-3,4-diols, we observed that (i) starting material **3** is easily accessible in multigram scale in a single reaction; (ii) reaction of **3** with indium in THF is fast, almost complete without using any excess of indium; and (iii) the addition to aldehydes is complete in a few hours at room temperature or lower, with a selectivity that mainly depends on the nature of the aldehyde, namely, conjugated or saturated.

Studies on further applications of **3** are in process.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of **5**−**7**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) Neuenschwander, M.; Bigler, P.; Christen, K.; Iseli, R.; Kyburz, R.; Mühle, H. *Helv. Chim. Acta* **1978**, *61*, 2047.

(21) (a) Li, C. J.; Chan, T. H. *Tetrahedron* **1999**, *55*, 11149. (b) Isaac, M. B.; Paquette, L. A. *J. Org. Chem.* **1997**, *62*, 5333. (c) Li, C. J. *Tetrahedron* **1996**, *52*, 5643. (d) Cintas, P. *SynLett.* **1995**, 1087.

(22) **Typical Procedure.** To a suspension of indium powder (0.115 g, 1 mmol) in THF (1 mL) was added 1-acetoxy-3-bromo-1-propene **3** (0.175 mL, 1.5 mmol) at 0 °C. The heterogeneous mixture was stirred for 30 min at 0 °C, the ice bath was removed, and stirring was continued for 3.5 h at room temperature. The aldehyde was added (1 mmol) at 0 °C, and the reaction mixture was stirred for 4 h at 0 °C.

(23) Augé, J.; Lubin-Germain, N.; Thiaw-Woaye, A. *Tetrahedron Lett.* **1999**, *40*, 9245. For other indium-catalyzed Barbier reactions in the presence of zinc or aluminum, see: (a) Steurer, S.; Podlech, J. *Adv. Synth. Catal.* **2001**, *343*, 251. (b) Araki, S.; Jin, S. J.; Idou, Y.; Butsugan, Y. *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1736.