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September 2014: The paragraphs above replace the section "Handling and Disposal of Hazardous Chemicals" in the originally published version of this article. The statements above do not supersede any specific hazard caution notes and safety instructions included in the procedure.

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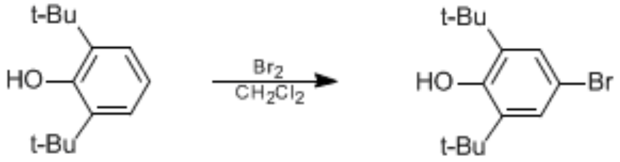
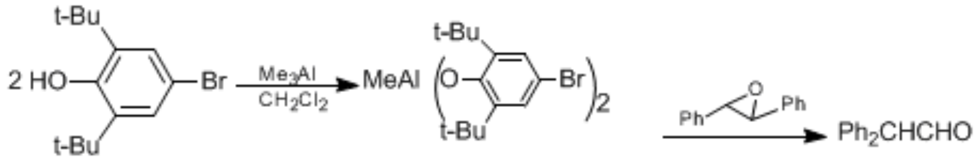
REARRANGEMENT OF trans-STILBENE OXIDE TO DIPHENYLACETALDEHYDE WITH CATALYTIC METHYLALUMINUM BIS(4-BROMO-2,6-DI-tert-BUTYLPHENOXIDE)

[Oxirane, 2,3-diphenyl-, trans- to Benzeneacetaldehyde, α-phenyl-]

A.



B.



Submitted by Takashi Ooi, Keiji Maruoka, and Hisashi Yamamoto[1].
Checked by Catherine Gasparski and Larry E. Overman.

1. Procedure

> *Caution! Dialkylzinc compounds, especially in undiluted form, are pyrophoric and must not be allowed to come into contact with air or moisture. These compounds should only be handled by individuals trained in their proper and safe use. [Note added January 2011]*

A. *4-Bromo-2,6-di-tert-butylphenol*. A dry, 1-L, three-necked, round-bottomed flask is fitted with a gas inlet, rubber septum, pressure-equalizing dropping funnel, magnetic stirring bar, and a gas outlet tube that is connected to a gas trap containing 0.5 M sodium hydroxide (NaOH). The flask is charged with 103.2 g (500 mmol) of 2,6-di-tert-butylphenol (Note 1) and flushed with argon, after which 200 mL of dry dichloromethane (Note 2) is added. The dropping funnel is charged with 28.2 mL (550 mmol) of bromine and 20 mL of dry dichloromethane. The reaction vessel is immersed in an ice-water bath, stirring is initiated, and bromine in dichloromethane is added over 1 hr. The reaction mixture is stirred at 0°C for 10–20 min (Note 3). Then 60 mL of saturated aqueous sodium sulfite is added slowly at 0°C and stirring is continued at room temperature until the light orange color of bromine is discharged, The mixture is poured into a 1-L separatory funnel containing 400 mL of saturated aqueous sodium bicarbonate (Note 4). The heavier organic layer is separated and the aqueous layer is extracted with two 75-mL portions of dichloromethane. The combined extracts are dried over sodium sulfate and concentrated with a vacuum rotary evaporator. The residue is recrystallized twice from ethanol-water (first with 130 mL of ethanol and 18 mL of water, then with 110 mL of ethanol and 11 mL of water) to furnish 109 g (76% yield) of 4-bromo-2,6-di-tert-butylphenol (Note 5) as light yellow crystals, mp 83–85°C. Pure 4-bromo-2,6-di-tert-butylphenol is reported to melt at 81–82°C.[2]

B. *Diphenylacetaldehyde*. A dry, 1-L, three-necked, round-bottomed flask is equipped with a gas inlet, rubber septum, pressure-equalizing dropping funnel, and a magnetic stirring bar. The flask is charged with 3.42 g (12 mmol) of 4-bromo-2,6-di-tert-butylphenol and flushed with argon, after which 600 mL of freshly distilled dichloromethane is added. The mixture is stirred, degassed under vacuum, flushed with argon, and 3 mL (6 mmol) of a 2 M hexane solution of trimethylaluminum (Me_3Al, (Note

6)) is injected through the septum to the flask at room temperature. The resulting solution is stirred at this temperature for 1 hr to give methylaluminum bis(4-bromo-2,6-di-tert-butylphenoxide) almost quantitatively (Note 7). The reaction vessel is cooled to a temperature of −20°C in a dry ice/o-xylene bath (Note 8). Then 11.8 g (60 mmol) of trans-stilbene oxide (Note 9) is dissolved in 25 mL of dry dichloromethane, transferred to the dropping funnel, and added over 15–20 min at −20°C. The mixture is stirred at −20°C for 4 hr. After addition of 1.01 g (24 mmol) of sodium fluoride, 324 μL (18 mmol) of water is injected dropwise at −20°C (Note 10). The entire mixture is vigorously stirred at −20°C for 5 min and at 0°C for 30 min. The contents of the flask are filtered with the aid of three 50-mL portions of dichloromethane (Note 11),(Note 12),(Note 13),(Note 14),(Note 15). The combined filtrates are concentrated to ca. 100 mL under reduced pressure with a rotary evaporator. Silica gel (35 g) is added and the remainder of the dichloromethane is removed using a rotary evaporator. The residue is layered on a column of silica gel (500 g, column diameter: 9.5 cm) (Note 12) and eluted (ether/dichloromethane/hexane, 1:2:20 to 1:1:10 as eluants) to give 10.3 g (87%) of diphenylacetaldehyde as a colorless oil (Note 16) and (Note 17).

2. Notes

1. 2,6-Di-tert-butylphenol was obtained from Nacalai Tesque Co. and used without any purification.
2. Solvent grade dichloromethane was dried and stored over Linde type 4 Å molecular sieves.
3. The reaction is conveniently followed by TLC (silica gel, 10:1:1 hexane-CH_2Cl_2-ether).
4. The extractive workup is performed carefully to avoid vigorous evolution of carbon dioxide gas.
5. The product has the following spectral properties: ^1H NMR (200 MHz, $CDCl_3$) δ: 1.39 (s, 18 H, 2 t-Bu), 5.15 (s, 1 H, OH), 7.24 (s, 2 H, Ar-H).
6. Neat trimethylaluminum was obtained from Toso-Akzo Chemical Company Ltd. (Japan) and used as a 2 M hexane solution. The checkers used similar material obtained from Aldrich Chemical Company, Inc.
7. During this operation, nearly 2 equiv of methane gas are evolved per 1 equiv of trimethylaluminum.
8. o-Xylene is recommended as refrigerant in place of carbon tetrachloride.
9. trans-Stilbene oxide was obtained from Aldrich Chemical Company, Inc., and used without any purification.
10. To avoid excessive foaming on hydrolysis water should be added carefully by syringe.
11. The sodium fluoride-water workup offers an excellent method for large-scale preparations, and is generally applicable to product isolation in the reaction of organoaluminum compounds.[3]
12. The checkers report that GLC analysis (Note 13) at this point shows that the product is contaminated with ca. 4% of trans-stilbene oxide and <1% of the Tischenko product (Note 14).
13. Gas chromatography conditions are as follows: Supelco fused silica capillary SPB-1 column (30 m, 0.32-mm ID, 0.25 micrometers df), 100°C initial temperature, 280°C final temperature, 10°C/min. The following retention times were obtained: diphenylacetaldehyde (6.7 min), trans-stilbene oxide (7.4 min), Tischenko product (18.2 min).
14. The Tischenko product, $Ph_2CHCO_2CH_2CHPh_2$, has the following properties: mp, 95–98°C, ^1H NMR (300 MHz, $CDCl_3$) δ: 4.35 (t, 1 H, J = 7.5), 4.70 (d, 2 H, J = 7.5), 4.92 (s, 1 H), 7.11–7.40 (m, 20 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ: 49.7, 57.2, 67.4, 126.8, 127.1, 128.2, 128.47, 128.53, 138.3, 140.8, 172.2; HRMS (CI, isobutane) Calcd for $C_{28}H_{24}O_2$: 393.1854 (MH); Found: 393.1829; IR (CCl_4) cm^{-1}: 3094–2906, 1737, 1600, 1494, 1450, 1144.
15. Merck Kieselgel 60 (Art. 9385) was used. The checkers found that loading the column in this way avoids precipitation of a by-product during column elution. The chromatography removes a few percent of remaining epoxide and 4-bromo-2,6-di-tert-butylphenol.
16. The product is >99% pure by capillary GLC analysis (Note 13) and has the following spectral characteristics: ^1H NMR (200 MHz, $CDCl_3$) δ: 4.92 (d, 1 H, J = 2.6, CH), 7.20–7.49 (m, 10 H, 2 Ph), 9.98 (d, 1 H, J = 2.6, CHO).
17. The rearrangement is considerably faster when the reaction solution is more concentrated. If 480 mL of dichloromethane is used, the rearrangement is complete within 20 min at −20°C. However, the checkers found that the crude product is contaminated with 3–10% of the Tischenko product (Note 14), which is difficult to remove by chromatography. This by-product can be removed by vacuum distillation

(bp 136–144°C, 2 mm). Using this combined purification procedure, the checkers obtained 9.6 g (81%) of diphenylacetaldehyde of >99% purity by capillary GLC analysis (Note 13).

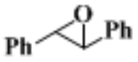
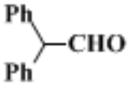
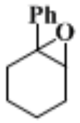
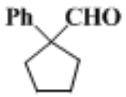
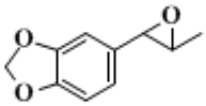
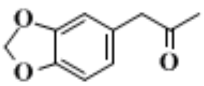
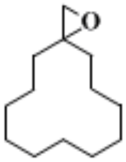
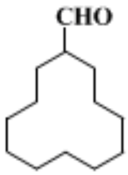
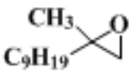
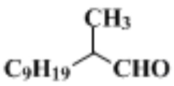
Waste Disposal Information

All toxic materials were disposed of in accordance with "Prudent Practices in the Laboratory"; National Academy Press; Washington, DC, 1995.

3. Discussion

This catalytic procedure illustrates a general method for preparing a wide range of carbonyl compounds by the selective rearrangement of epoxides under the influence of the exceptionally bulky, oxygenophilic methylaluminum bis(4-bromo-2,6-di-tert-butylphenoxide) (MABR) as catalyst.[4] The advantages of catalytic versions include economy, ease of large-scale preparation and isolation, and the synthetic potential for in situ derivatization of the carbonyl products. Use of a sodium fluoride-water ($NaF-H_2O$) workup[3] further simplifies the experimental operation. As revealed in Tables I and II, the amount of the catalyst varies from 5 to 20 mol% depending on the epoxy substrates. Yields when MABR is used stoichiometrically are also included for comparison. Certain epoxy substrates require stoichiometric MABR. Neither epoxides derived from monsubstituted olefins nor from certain internal dialkyl-substituted olefins can be rearranged by MABR, however, even using two equivalents.

TABLE I
MABR-Catalyzed Rearrangement of Epoxides

Epoxide	MABR (mol %)	Product	Yield (%)
	200		93
	10		95
	200		98
	10		96
	5		91
	200		87
	10		90
	5		84
	200		94
	20		58
	200		96
	20		0
	200		73

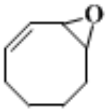
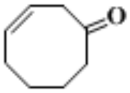
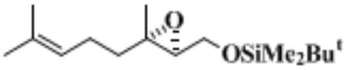
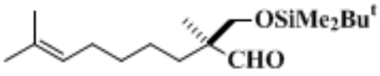
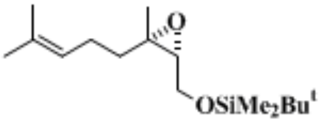
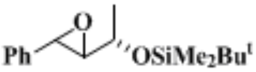
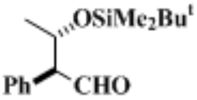
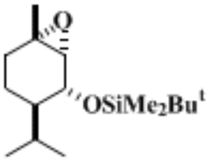
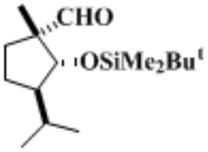
	20		0

TABLE II
MABR-CATALYZED REARRANGEMENT OF CHIRAL EPOXY SILYL ETHERS

Epoxy Silyl Ether	MABR (mol %)	β-Siloxy Aldehyde	Yield (%)
	200 20 10		99 82 74
	200 20 10		98 79 68
	200 20 10		87 74 71
	200 20		88 77

The MABR-promoted rearrangement, when applied to optically active epoxy substrates, has been shown to proceed with rigorous transfer of the epoxide chirality. Accordingly, used in combination with the Sharpless asymmetric epoxidation of allylic alcohols,[5] this rearrangement represents a new approach to the synthesis of various optically active β-siloxy aldehydes, useful intermediates in natural product synthesis (Table II).[4,6]

The stronger coordination of a carbonyl oxygen than an epoxide oxygen to an aluminum reagent requires the stoichiometric use of MABR at low temperature. The key element of the present modification is the use of a higher reaction temperature (though still at or below 0°C) than the previously reported conditions[7] in order to induce dissociation of the aluminum reagent-carbonyl complex, thereby allowing regeneration of MABR as catalyst for further use in the catalytic cycle of the reaction. The facile dissociation of the organoaluminum-carbonyl complex as well as the smooth rearrangement of epoxides is apparently ascribable to the exceptional bulkiness of MABR compared to other ordinary Lewis acids.[8] The less bulky methylaluminum bis(4-bromo-2,6-diisopropylphenoxide) was found to be totally ineffective for the rearrangement of the tert-butyldimethylsilyl ether of epoxy geraniol.

References and Notes

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Appendix
Chemical Abstracts Nomenclature (Collective Index Number); (Registry Number)

methylaluminum bis(4-bromo-2,6-di-tert-butylphenoxide) (MABR)

Dry Ice

ethanol (64-17-5)

ether (60-29-7)

sodium sulfite (7757-83-7)

sodium hydroxide (1310-73-2)

sodium bicarbonate (144-55-8)

bromine (7726-95-6)

sodium sulfate (7757-82-6)

oxygen (7782-44-7)

carbon tetrachloride (56-23-5)

carbon dioxide (124-38-9)

methane (7782-42-5)

dichloromethane (75-09-2)

sodium fluoride (7681-49-4)

hexane (110-54-3)

argon (7440-37-1)

Diphenylacetaldehyde,
Benzeneacetaldehyde, α-phenyl- (947-91-1)

trimethylaluminum (75-24-1)

trans-Stilbene oxide,
Oxirane, 2,3-diphenyl-, trans- (1439-07-2)

Methylaluminum bis(4-bromo-2,6-di-tert-butylphenoxide) (118495-99-1)

4-Bromo-2,6-di-tert-butylphenol (1139-52-2)

2,6-di-tert-butylphenol (128-39-2)

o-Xylene (95-47-6)

Methylaluminum bis(4-bromo-2,6-diisopropylphenoxide)

tert-butyldimethylsilyl ether

epoxy geraniol