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Regio- and stereoselective reductive opening of diene-ester derived monoepoxides with palladium catalyst and dimethylamine–borane complex

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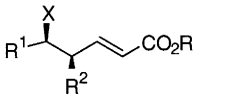
Abstract

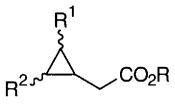
Monoepoxides of diene-esters are regio- and stereoselectively reduced to homoallylic alcohols by dimethylamine–borane complex in the presence of acetic acid and catalytic amounts of $Pd(PPh_3)_4$.

Keywords: palladium catalysis; amine–borane complexes; epoxide hydrogenolysis.

In relation with our current study[1] on the SmI_2-induced cyclisation of δ-halo-α,β-unsaturated esters to cyclopropane compounds **2**, we needed to prepare, as precursors to these homoallylic halides **1a**, homoallylic alcohols **1b** with various substituent patterns and with high diastereoselectivity in cases where both homoallylic and allylic positions were substituted (R^1 and $R^2 \neq H$). To obtain these alcohols, we decided to rely on the palladium-catalysed hydrogenolysis of vinyl epoxides with formic acid in the presence of triethylamine, as described[2] by Tsuji, Shimizu and co-workers. These reactions, which involve the intermediate formation of π- and/or σ-allyl complexes are generally regioselective (leading to homoallylic alcohols rather than allylic alcohols) and also stereospecific as they give the product of inversion of configuration at the allylic C–O bond. Such stereoselectivity stems from the fact that hydride delivery from the intermediate formato-π- or σ-allylic complexes occurs from the palladium side, probably through a concerted cyclic mechanism[3] (Eq. (1)).



1 a: X = I, Br; **b**: X = OH



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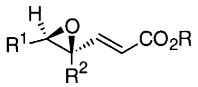

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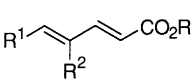

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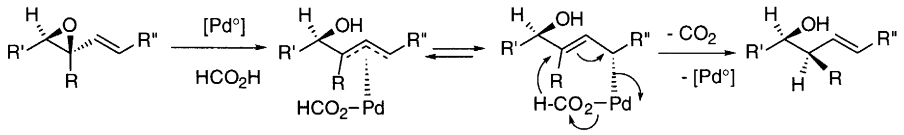
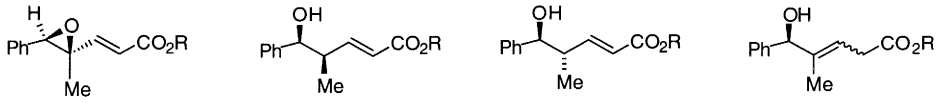


(1)

Epoxides **3** are easily available in racemic form by controlled, regioselective monoepoxidation of diene-esters **4** with MCPBA, and recently, Shi and co-workers[4] reported a very efficient enantioselective synthesis of such diene-monoepoxides by use of a fructose-derived chiral ketone as catalyst and oxone as oxidant.

In complete concordance with Tsuji and Shimizu's observation, we found that the palladium-catalysed hydrogenolysis of epoxides **3** was totally regioselective and, in the case of substituted allylic substrates ($R^2 \neq H$), stereoselective. Meanwhile, we were unable to reproduce the high overall yields reported by these authors, especially in the case of the substituted allylic epoxides. For instance, in our hands, homoallylic alcohol **6** was indeed obtained, from epoxyenoate **5** (R=Bn**)**, as the sole product in significant amount and to the exclusion of diastereoisomer **7** and allylic alcohol **8**, but only in 28–30% overall yield instead of the 98% yield reported for the corresponding methyl ester (R=Me) by Shimizu, Tsuji and co-workers. Purification of **6** from many minor impurities by column chromatography proved to be tedious.



5 **6** **7** **8**

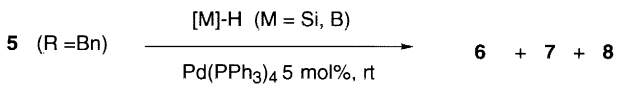
We recently reported the efficient palladium cleavage of allylic carboxylates and carbamates in the presence of several pseudometallic hydrides, especially phenylsilane[5,6] and ammonia- or dimethylamine–borane complexes[6] and the application of such systems in protective group chemistry. We therefore decided to test these hydride donors as well as sodium borohydride[3,7] in the reductive opening of vinyl epoxides **3**. As test reaction, we selected the reductive opening of epoxide **5**. Our results are reported in Table 1. Yields refer to isolated products after chromatography. The two diastereoisomeric homoallylic alcohols **6** and **7** could not be separated by this technique; their ratio was measured by ^{1}H NMR spectroscopy.[8]

Examination of entries 1–5 shows that better overall yields were obtained with the pseudometallic hydrides under study than with formic acid. However, the reactions were no longer selective and mixtures of both diastereoisomeric homoallylic alcohols **6** and **7** and of an allylic alcohol **8**, whose stereochemistry was not elucidated, were most of the time obtained. Meanwhile, compared to sodium borohydride, better results were obtained with amine–borane complexes. In the best case (Me_2NH–BH_3, entry 3), the reaction was regioselective (no allylic alcohol) but its diastereoselectivity (**6**/**7**=87/13) was still unsatisfactory.

Noting that the excellent regio- and stereoselectivities reported by the Japanese authors were obtained in acidic medium (since in their procedure formic acid is used in excess over triethylamine), we decided to repeat our reactions with pseudo-metallic hydrides in the presence of acetic acid. Indeed, since the formation of π- or σ-allyl complexes from palladium(0) and vinyl epoxides also results in unmasking alkoxide function, it could be expected that the reactivity of these intermediates would be greatly modified in the presence of a protonating agent. To our satisfaction, we found that, under such conditions, the reactions were greatly improved (entries 6–8) in terms of rapidity, overall yield and selectivity. In particular, with the dimethylamine–borane complex, homoallylic alcohol **6** was obtained selectively and in almost quantitative yield within 15 min at room temperature.

The effectiveness of the palladium/Me_2NH–BH_3/AcOH system[9] was confirmed on a series of monoepoxides **9** derived from diene-esters as represented in Table 2.

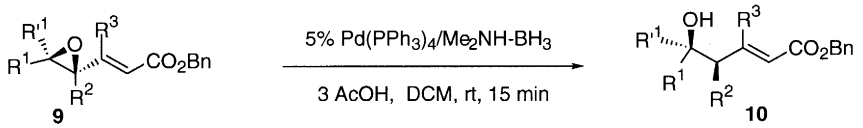
Table 1



Entry	Hydride[a]	Solvent	Additive	reaction time	yield (%) 6+7	ratio 6/7	Yield (%) 8
1	$PhSiH_3$	DCM	none	4 h	53	80/20	37
2	H_3N-BH_3	DCM	none	15 min.	72	70/30	15
3	Me_2NH-BH_3	DCM	none	15 min.	78	87/13	traces
4	$PhSiH_3$	THF	none	4 h.	41	70/30	28
5	$NaBH_4$	THF	none	15 min	60	66/33	0
6	$PhSiH_3$	DCM	AcOH[b]	1 h.	74	>95/5[c]	4
7	H_3N-BH_3	DCM	AcOH[b]	15 min.	85	92/8	0
8	Me_2NH-BH_3	DCM	AcOH[b]	15 min.	96	>95/5[c]	0

[a] 1.1 *molar* equivalents in every case ; [b] 3 equiv. of AcOH were used; [c] 7 was not detected by NMR.

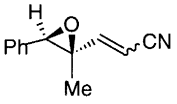
Table 2



Entry	R^1	R'^1	R^2	R^3	Yield (%)[a,b]
1	H	H	H	H	90 (81)
2	Me	H	H	H	89 (72)
3[c]	H	H	Me	H	91 (41[d])
4	H	H	H	Me	91
5	Me	H	Me	H	92 (55)
6	Me	Me	H	H	97

[a]Isolated yields; for comparison, yields that we obtained following the Tsuji/Shimizu procedure [5% $Pd(dba)_2$, 2.5% PPh_3, 3 equiv. Et_3N, 6 equiv. HCO_2H, rt, 6h] are indicated in brackets. [b] Unless otherwise specified, homoallylic alcohol **10** was selectively obtained to the exclusion of its diastereoisomer and of allylic alcohol. [c] **9** in its racemic form. [d] 7% of allylic alcohol was also obtained.

Finally, we also studied the reductive opening of epoxide **13** derived from a dienenitrile and consisting (NMR) of a 7/3 mixture, respectively, of *E* and *Z* isomers. The reaction was no longer regioselective as it led to 30% of allylic alcohol **16** whose stereochemistry was not determined. In addition, 66% of two homoallylic alcohols were produced in a 7/3 ratio, both with *E* geometry of the double bond and to which we tentatively assign the respective structures **14** and **15**.[10,11] Compound **15** would therefore arise from reduction of *Z*-**13** with a π–σ–π interconversion of the intermediate π-allylic complexes. Such a process that results in retention of configuration at the allylic site and inversion of geometry of the double bond is well-documented in palladium-π-allyl chemistry[12] in general and, in particular, was evidenced in the reductive ring-opening of vinyloxirane with formic acid.[2]



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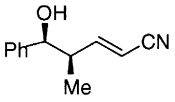

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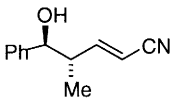

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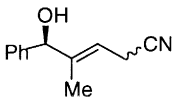

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In conclusion, the palladium-catalysed reductive opening of diene-ester derived monoepoxides by the ternary system $Pd(PPh_3)_4/Me_2NH\text{-}BH_3/AcOH$ leads to homoallylic alcohols with excellent regioselectivity and stereospecificity. This procedure, which is very easily carried out, is faster and in our hands gave better results than the corresponding palladium-catalysed hydrogenolysis with formic acid as described by Tsuji, Shimizu and co-workers.

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8. ^{1}H NMR ($CDCl_3$, 250 MHz): **6**: 7.40–7.28 (m, 10H); 7.07–6.98 (dd, ^{3}J=16.0 and 7.5 Hz, 1H); 5.89–5.82 (dd, ^{3}J=16.0 Hz, ^{4}J=1 Hz, 1H); 5.17 (s, 2H); 4.70 (broad d, J=5.5 Hz, 1H, benzylic H); 2.77 (broad sext., J=7 Hz, 1H, allylic H); 2.40 (d, J=ca. 1–2 Hz, 1H, OH); 1.09 (d, ^{3}J=7.0 Hz, 3H). Compound **7**: 7.40–7.28 (m, 10H); 7.17–7.07 (dd, ^{3}J=15.5 and 8 Hz, 1H); 6.00–5.94 (dd, ^{3}J=15.5 Hz, ^{4}J=1 Hz, 1H); 5.20 (s, 2H); 4.51 (broad d, J=7.5 Hz, 1H, benzylic H); ca. 2.70 (broad sext., 1H, allylic H); 2.50 (broad s, 1H, OH); 0.92 (d, ^{3}J=7 Hz, 3H). Compound **8**: 7.40–7.28 (m, 10H); 5.68 (s, 1H, allylic-benzylic H); 5.58 (t, ^{3}J=7.5 Hz, 1H, vinylic H); 5.17 (s, 2H); 3.19–3.15 (broad m, 2H); 1.78 (broad s, 3H).
9. Reactions were conducted in degassed solvents and under argon and monitored by TLC. Typical experimental procedure: a 10 mL dichloromethane (DCM) solution of 1.75 g (5.95 mmol) of epoxide **5** (R=Bn) and 1.02 mL (3 equiv.) of AcOH was syringed through a rubber septum cap into a flask containing a freshly prepared solution of 0.34 g (5×10^{-2} molar equiv.) of $Pd(PPh_3)_4$ and 0.385 g (1.1 equiv.) of dimethylamine–borane complex and the reaction mixture was stirred at room temperature for 15 min. The solvent was evaporated and the residue was directly purified by column chromatography to give 1.67 g (95%) of pure homoallylic alcohol **6**.
10. ^{1}H NMR ($CDCl_3$, 250 MHz): **14**: 7.37–7.22 (m, 5H); 6.70–6.60 (dd, ^{3}J=16.5 and 7.5 Hz, 1H); 5.25–5.18 (dd, ^{3}J=16.5 Hz, ^{4}J=1 Hz, 1H); 4.58 (broad d, ^{3}J=5.5 Hz, 1H, benzylic H); 2.93 (d, J=ca. 3.5 Hz, 1H, OH), 2.66 (broad sext., J=6.5 Hz, 1H, allylic H); 1.03 (d, ^{3}J=7 Hz, 3H). Compound **15**: 7.37–7.22 (m, 5H); 6.83–6.73 (dd, ^{3}J=16.5 and 8 Hz, 1H); 5.32–5.25 (dd, ^{3}J=16.5 Hz, ^{4}J=1 Hz, 1H); 4.45 (broad d, J=7 Hz, 1H, benzylic H); 2.95 (d, J=ca. 2.0 Hz, 1H, OH); ca. 2.63 (broad sext., J=7 Hz, 1H, allylic H); 0.94 (d, ^{3}J=7 Hz, 3H).
11. Allylic alcohol **16** was the main product of reaction when $PhSiH_3$ was used as the hydride donor.
12. See for example: Trost, B. M.; Van Vranken, D. L. *Chem. Rev*. **1996**, *96*, 395–422.