Palladium(II)-catalysed Asymmetric Acetalization of Alkenes

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Methacrylamide bearing 4-*tert*-butyloxazolidin-2-one as a chiral auxiliary reacts with methanol in the presence of $PdCl_2$ catalyst to give the corresponding acetal in 95% diastereoisomeric excess, and removal of the auxiliary results in the formation of chiral acetals.

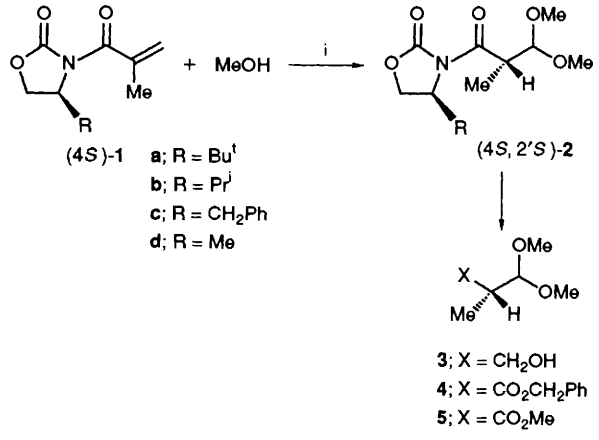
The use of chiral acetals in synthetic organic chemistry has developed into modern stereoselective reactions.[1] Since acetals previously prepared from carbonyl compounds are now obtainable from alkenes by using palladium(II) catalysts,[2] synthetic methods for acetals have been expanded. Undoubtedly, stereoselective synthesis of chiral acetals from alkenes provides a novel entry to asymmetric reactions. We report here, for the first time, the highly, diastereoselective acetalization of alkenes with alcohols.

As shown in Table 1, the acetalization of (4*S*)-*N*-methacryloyl-*tert*-butyloxazolidin-2-one **1a** (R = Bu^t) with methanol affords a 95% diastereoisomeric excess (d.e.) of acetal **2a** in

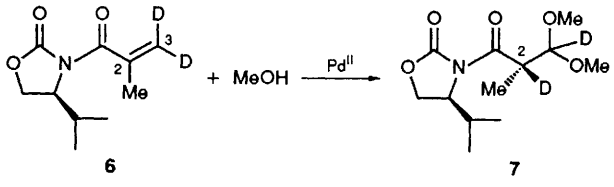
Table 1 Pd^{II}-catalysed acetalization of **1** with alcohols[a]

Entry	Substrate	R	Alcohol (equiv.)	T/°C[b]	t/h	Acetal **2** Yield (%)[c]	Acetal **2** D.e. (%)[d]
1	**1a**	Bu^t	MeOH (25)	r.t.	90	89	95
2	**1b**	Pr^i	MeOH (25)	r.t.	96	66	61
3	**1c**	CH_2Ph	MeOH (25)	r.t.	96	30[e]	32
4	**1d**	Me	MeOH (25)	r.t.	29	61	23
5	**1b**	Pr^i	MeOH (10)	50	23	72	43
6	**1b**	Pr^i	Pr^nOH (10)	50	24	75[e]	48

[a] The reaction was performed by using substrate **1** (0.5 mmol) $PdCl_2$ (0.05 mmol), and CuCl (0.5 mmol) under O_2 (1 atm, balloon) in 1,2-dimethoxyethane (DME) (1 ml). [b] r.t. = room temperature. [c] Isolated yield unless otherwise noted. [d] Determined by ^1H NMR and GLC analyses (capillary column OV-1 bonded, 1 mm × 25 m). [e] Determined by ^1H NMR analysis.



Scheme 1 *Reagents and conditions*: i, $PdCl_2$ (10 mol%) CuCl (1 equiv.), O_2

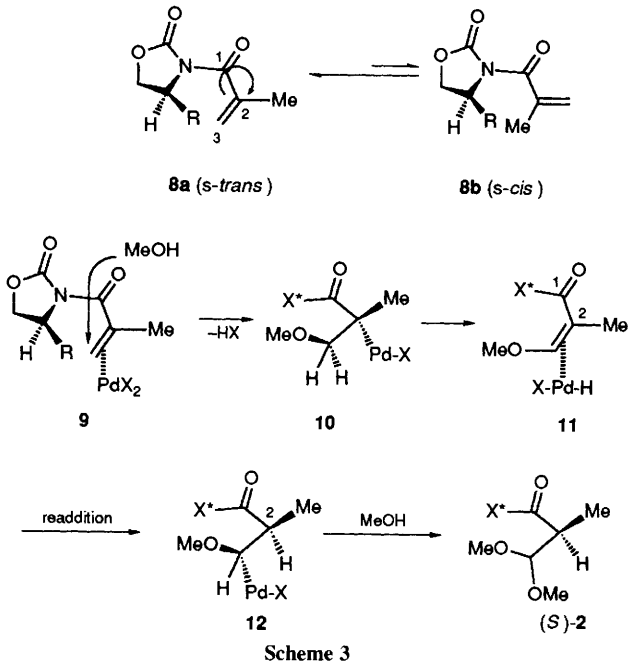


Scheme 2

89% isolated yield (entry 1). Steric bulkiness of substituents (R) on the oxazolidinone moiety of **1** affects the stereoselectivity of the acetalization. The decrease in d.e. follows in the order of R = Bu^t (95%), Pr^i (61%), $PhCH_2$ (32%) and Me (23%) (entries 1–4). At higher temperature (50 °C), the reaction proceeds faster, but as expected the selectivity is decreased down to 43% d.e. (entry 5). When propan-1-ol was used in place of methanol, no particular change was observed (entry 6).

When obtained acetal **2b** was treated with $LiAlH_4$, hydroxyacetal **3** was formed in 89% yield with no loss of enantiomeric purity. The absolute configuration of **3** formed was found to be (*R*) by comparing its $[\alpha]_D$ value with that of the authentic sample prepared from commercially available methyl (*S*)-(+)-3-hydroxy-2-methylpropionate.† Accordingly, the newly created chiral centre of **2** in the present acetalization is assigned as (*S*). Recrystallization of the acetal **2a** from hexane–diisopropyl ether affords pure diastereoisomer, from which optically pure acetal ester **4** or **5** can be obtained, upon treatment with either $PhCH_2OLi$ or

† The authentic compound was prepared as follows; (*i*) protection of the OH group of (*S*)-2-methoxycarbonylpropanol by Bu^tMe_2SiCl, (*ii*) diisobutylaluminium hydride (DIBAL) reduction, (*iii*) Swern oxidation, (*iv*) acetalization with 2,2-dimethoxypropane using $BF_3{\cdot}(Et_2O)$ and (*v*) deprotection of the silyl group.



Scheme 3

LiOOH and CH_2N_2, with >95% recovery of the chiral auxiliary.

To study the mechanistic details of the present, asymmetric acetalization we have prepared dideuteriated alkene **6** bearing 4-isopropyloxazolidin-2-one moiety from [1,1-$^2H_2$]methyl methacrylate.[3] The acetalization of **6** with methanol at 50 °C afforded **7** (82% yield, 50% d.e.), which arises from a process involving the D-atom migration from the terminal olefinic carbon to the C-2 carbon. The D-atom content of **7** judging from the ^1H NMR and mass spectra was ~90%, and thus no substantial D-loss took place during the reaction. Furthermore, when the acetalization of **1b** (R = Pr^i) was carried out in MeOD, virtually no D-atom incorporation was observed in the product.

On the basis of these results, the mechanism of the acetalization of **1** can be rationalized as shown in Scheme 3. The conformational preference about the C-1–C-2 bond of **1** must be the s-*trans* form **8a** rather than the s-*cis* **8b**, because of the steric interference between the Me substituent on the olefin and the R group on the chiral auxiliary. An MM2 calculation using the Tektronix Cache system supports this view. The rotation about the C-1–N bond will be fixed *via* chelation of carbonyl groups to metal salts present. Coordination of Pd^{II} to the less hindered side of the olefin followed by nucleophilic attack of MeOH to **9** in a *trans* fashion gives the oxypalladation adduct **10**. Subsequent β-hydride elimination leads to vinyl ether complex **11**. Readdition of Pd–H species to the vinyl ether from the same face creates the chiral centre at the C-2 carbon, and the C–Pd bond formed is then displaced

by MeOH[4] to give the acetal **2** of (*S*) configuration.‡ Therefore, the stereoselective 1,2-hydride migration is one of the crucial factors in the present, asymmetric reaction. Addition of MeOH to the vinyl ether **11**, if it is free, would afford the acetal **2**. If this is the case, the D-atom of MeOD would be incorporated into the product. However, the experimental result does not agree with this. The 1,2-hydride migration has been observed in Pd^{II}-catalysed acetalization of styrene and phenyl vinyl ketones with diols.[2a]

In brief, the mechanistic study reveals that the reaction involves *trans*-oxypalladation and 1,2-stereoselective hydride migration, if the view about the rotational preferences of the substrate is valid. Furthermore, the present transformation of **1** to acetals **2** of aldehyde precursors is regarded as a novel class of asymmetric oxidation of alkenes which has received little attention.

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‡ Alternatively, methoxypalladation towards **11** with loss of HX followed by reductive elimination affords the acetal **2**. Details of these will be reported in the future.

References

1 A. Alexakis and P. Mangeney, *Tetrahedron Asymmetry*, 1990, **1**, 477; S. E. Denmark and N. G. Almstead, *J. Am. Chem. Soc.*, 1991, **113**, 8089 and references cited therein.
2 (*a*) T. Hosokawa, T. Ohta, S. Kanayama and S.-I. Murahashi, *J. Org. Chem.*, 1987, **52**, 1758; (*b*) T. Hosokawa and S. I. Murahashi, *Acc. Chem. Res.*, 1990, **23**, 54.
3 M. Mihailov, S. Dirilikov, N. Peeva and Z. Georgiva, *Macromolecules*, 1974, **176**, 789.
4 H.-B. Lee and P. M. Henry, *Can. J. Chem.*, 1976, **54**, 1726.