Catalytic asymmetric synthesis of optically active alkenes by palladium-catalysed asymmetric reduction of racemic allylic esters with formic acid

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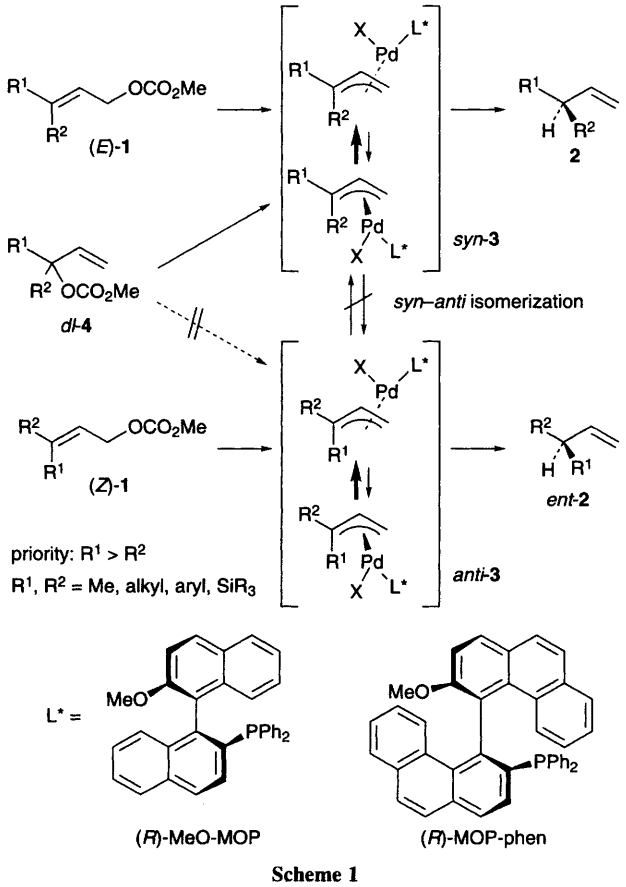
Asymmetric reduction of racemic allyl esters, *e.g.* methyl 1-vinyl-1,2,3,4-tetrahydronaphth-1-yl carbonate, which contain two different alkyl groups at the α-position, with formic acid in the presence of 1 mol% of palladium catalyst coordinated with (*R*)-3-diphenylphosphino-3′-methoxy-4,4′-biphenanthryl [(*R*)-MOP-phen] ligand gives optically active terminal alkenes in up to 93% ee.

It has been reported that the palladium-catalysed reduction of allylic carbonates **1** with formic acid[1] in the presence of a palladium catalyst coordinated with axially chiral monodentate phosphine ligand, (*R*)-2-diphenylphosphino-2′-methoxy-1,1′-binaphthyl [(*R*)-MeO-MOP],[2] or its biphenanthryl analogue, (*R*)-MOP-phen,[3] gave optically active alkenes **2** in up to 91% ee (Scheme 1).[4,5,6] The reduction proceeds by way of $Pd^{II}X(\pi$-allyl)(L*) intermediates **3** which undergo epimerization but do not undergo *syn–anti* isomerization, and the stereochemical outcome is determined by the thermodynamic stability of the epimeric π-allylpalladium intermediates.[3,4,5] The esters of 3,3-disubstituted prop-2-enols hitherto used for the asymmetric reduction are limited to those with a geometrically pure *E*- or *Z*-double bond for the high enantioselectivity becasue opposite enantiomers are produced from the *E*- and *Z*-esters. The palladium-catalysed reduction of racemic 1,1-disubstituted prop-2-enyl ester **4**, which is a regioisomeric ester of **1**, should proceed through the same π-allylpalladium intermediate **3**. If the oxidative addition of ester **4** to palladium(0) takes place with high selectivity in forming either the *syn* or *anti* π-allylpalladium intermediate, the reduction product **2** is expected to have enantiomeric purity, as high as that from the regioisomer (*E*)-**1** or (*Z*)-**1**. We found that the high enantioselectivity is attained with some racemic tertiary allylic esters **4** where one of the alkyl groups at the 1 position is bulky enough to bring about high *syn* selectivity at the oxidative addition step.

The results obtained for the asymmetric reduction of racemic esters **4** are summarized in Table 1, which also contains data for the reaction of (*E*)-**1** for comparison. The reduction of methyl 1-vinyl-1,2,3,4-tetrahydronaphth-1-yl carbonate **4a** with formic acid (2.2 equiv.) in the presence of proton sponge (1.2 equiv.) and 1.0 mol% of palladium catalyst, generated *in situ* by mixing

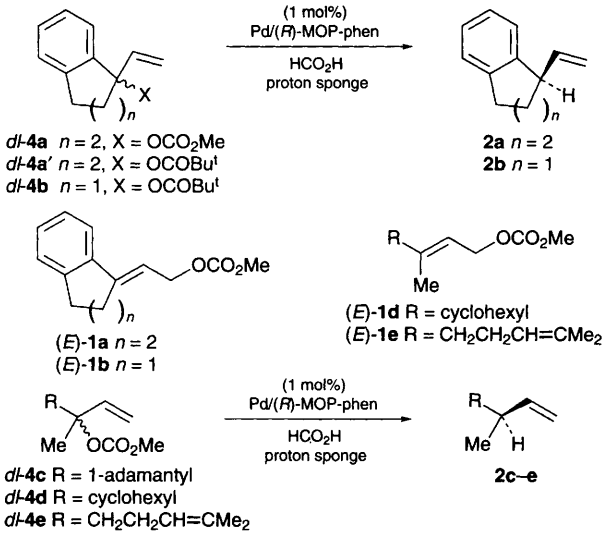


Scheme 1

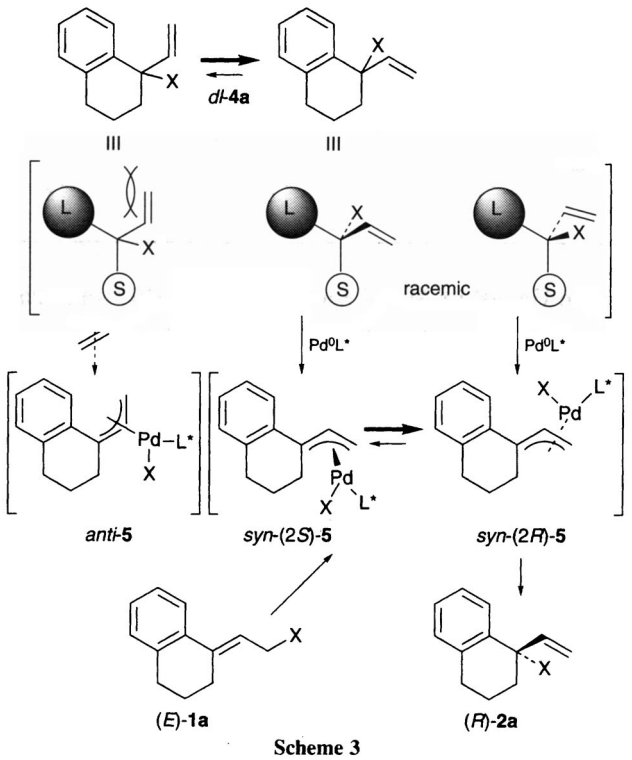
Table 1 Asymmetric reduction of allylic esters **4** or **1** with formic acid catalysed by palladium/MOP-phen[a]

Entry	Allyl ester	Conditions T/°C	Conditions t/h	Yield (%)[b] of **2**	Ee (%) of **2** (Config.)
1	*dl*-**4a**	−20	48	87 (**2a**)	93[c] (*R*)[d]
2	*dl*-**4a**	0	24	91 (**2a**)	91[c] (*R*)
3	*dl*-**4a**	20	5	87 (**2a**)	84[c] (*R*)
4[e]	*dl*-**4a**	20	12	89 (**2a**)	78[c] (*R*)
5	*dl*-**4a′**	−20	96	90 (**2a**)	92[c] (*R*)
6	*dl*-**4a′**	−20	48	45 (**2a**)[f]	91[c] (*R*)
7	(*E*)-**1a**	0	120	0 (**2a**)	—
8	(*E*)-**1a**	20	12	91 (**2a**)	83[c] (*R*)
9	*dl*-**4b**	0	24	81 (**2b**)	86[c] (*R*)[d]
10	(*E*)-**1b**	20	11	88 (**2b**)	78[c] (*R*)
11	*dl*-**4c**	0	36	96 (**2c**)	75[d,g]
12	*dl*-**4d**	20	3	92 (**2d**)	13[g] (*R*)
13[h]	(*E*)-**1d**	20	22	96 (**2d**)	85[g] (*R*)
14	*dl*-**4e**	20	12	>99 (**2e**)	8[i] (*S*)
15[h]	(*E*)-**1e**	20	17	>99 (**2e**)	85[i] (*S*)

[a] The reduction was carried out with 2.2 equiv. of formic acid in THF–dioxane (1:1) in the presence of 1.2 equiv. of 1,8-bis(dimethylamino)-naphthalene and 1.0 mol% of catalyst prepared *in situ* by mixing $Pd_2(dba)_3{\cdot}CHCl_3$ and MOP-phen (2 equiv. to Pd). [b] Isolated yield by silica gel column chromatography. [c] Determined by GLC analysis with chiral stationary phase column, CP Cyclodex β236M. [d] Specific rotations of **2a** (entry 1), **2b** (entry 9) and **2c** (entry 11) are $[\alpha]_D^{20}$ −84.0, −74.6 and +3.5 (*c* 0.9–1.0, chloroform), respectively. [e] Reaction with (*R*)-MeO-MoP. [f] The recovered (48%) ester **4a′** was racemic, which was determined by the GLC analysis (CP Cyclodex β236M) of 1-vinyl-1,2,3,4-tetrahydronaphthol. [g] Determined by HPLC analysis of anilide of carboxylic acid, obtained by the oxidation ($NaIO_4$–$KMnO_4$) of **2c** or **2d**, with Sumichiral OA- 2000 (hexane–dichloroethane–ethanol = 250:20:1). [h] Reported in ref. 4. [i] Determined by HPLC analysis of dianilide of 2-methylpentane- dioic acid, obtained by the oxidation ($NaIO_4$–$KMnO_4$) of **2e**, with Sumichiral OA-4100 (hexane–dichloroethane–ethanol = 50:15:1).



Scheme 2



Scheme 3

$Pd_2(dba)_3{\cdot}CHCl_3$ and (*R*)-MOP-phen (Pd/P = 1/2), proceeded at −20 °C in THF–dioxane to give the optically active (*R*)-1-vinyl-1,2,3,4-tetrahydronaphthalene **2a** in 87% yield {$[\alpha]_D^{20}$ − 84.0 (*c* 0.9, chloroform)} (Table 1, entry 1) (Scheme 2). The absolute configuration was assigned by correlation with known (*S*)-(−)-1,2,3,4-tetrahydronaphthoic acid[7] {$[\alpha]_D^{20}$ − 56.7 (*c* 0.5, benzene)} and the enantiomeric purity was determined to be 93% ee by capillary GLC analysis with a chiral stationary phase column, CP Cyclodex β-236M. The asymmetric reduction of *dl*-**4b**, which is a racemic ester derived from 1-indanone, also proceeded with high enantioselectivity giving the corresponding terminal alkene (*R*)-**2b**[8] in 86% ee (entry 9).

Interestingly the asymmetric reduction of *dl*-**4a** is much faster than that of its regioisomeric ester, 3,3-disubstituted prop-2-enyl carbonate (*E*)-**1a**. The reduction of (*E*)-**1a** did not take place at 0 °C or lower (entry 7). At 20 °C it gave (*R*)-**2a** in 83% ee (entry 8), the stereoselectivity being essentially the same as that for *dl*-**4a** at 20 °C (entry 3). The lower reactivity of (*E*)-**1a** is ascribed to the two alkyl substituents at the 3 position of (*E*)-**1a**. The steric hindrance retards the oxidative addition step in the catalytic cycle which takes place in an S_N' manner.[6,9]

The stereochemical results of the reduction of *dl*-**4a** and (*E*)-**1a** is illustrated in Scheme 3. The π-allylpalladium intermediate resulting from (*E*)-**1a** should be *syn*-**5**, which contains the aromatic ring at the *syn* position with respect to the hydrogen at the 2 position of π-allyl. The same stereochemical outcome in the reaction of (*E*)-**1a** and *dl*-**4a** indicates that the π-allylpalladium intermediate formed from *dl*-**4a** is also *syn*-**5**, and the configuration *R* of the product **2a** indicates that the configuration of the predominant π-allylpalladium intermediate is *syn*-(2*R*)-**5**[10] in both cases. In the reaction of racemic 1,1-disubstituted prop-2-enyl ester *dl*-**4** where one of the substituents on the 1-position is much bigger than the other, the allyl ester undergoes oxidative addition with the conformation forming a π-allylpalladium intermediate with the bigger alkyl group substituted at the *syn* position. After the epimerization between *syn*-(2*R*)-**5** and *syn*-(2*S*)-**5** the product (*R*)-**2a** is formed from the thermodynamically more stable *syn*-(2*R*)-**5** (Scheme 3).

The asymmetric reduction of acyclic allylic ester *dl*-**4c** that contains the sterically bulkyl 1-adamantyl group at the 1-position also proceeded with high enantioselectivity to give **2c** in 75% ee (entry 11). Much lower enantioselectivity (around 10% ee) was observed in the reaction of sterically less bulky esters *dl*-**4d** and *dl*-**4e** (entries 12 and 14). Comparing the low selectivity in the reaction of *dl*-**4d** and *dl*-**4e** with the high selectivity in the reaction of their regioisomers, (*E*)-**1d** and (*E*)-**1e**, which gave the corresponding alkenes[11] of 85% ee[4] (entries 13 and 15), it follows that the selectivity of the π-allylpalladium intermediates is low with these sterically less bulky 1,1-disubstituted prop-2-enyl esters.

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