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Asymmetric alkylidenecyclopropanes from the regioselective reduction of π 1,1-dimethyleneallyl palladium complexes

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Abstract: Palladium(0) catalyzed hydrogenolysis of (1*R*,2*S*)-1-(1-alkenyl)-2-methylcyclopropyl mesylate **6b** led to (E)-(2*S*)-alkenylidene(2-methylcyclopropanes), regioselectively, depending on the steric effect of trivalent phosphorus palladium ligands.
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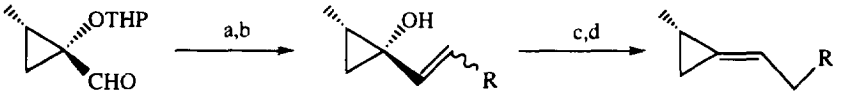
Cyclopropane derivatives provide building blocks of unprecented synthetic potential.[1–4] In particular alkylidenecyclopropanes form a special class of strained olefinic compounds, which offer enormous potential in organic synthesis;[5,6] thus, they undergo ring opening with palladium chloride to produce π-allyl palladium complexes,[7] carbopalladation with vinyl- and arylhalides in the presence of Pd(0),[8] regioselective Pd(0) catalyzed [3+2] cycloaddition with olefinic and acetylenic substrates,[5,9] Pauson Khand cyclization with dicobalt hexacarbonyl complexes of acetylene,[10] 1,3-dipolar cycloaddition with nitrones.[11] Most of these reactions have been reported to occur both inter- and intramolecularly.[8,11] Moreover, alkylidenecyclopropanes constitute the most suitable precursors for cyclobutanone synthesis.[2,12] As many cyclopropane derivatives, they are also endowed with specific bioactivities.[13] As far as we know, chiral alkylidenecyclopropanes have not been prepared and used in their optically active form. We report now a convenient route to these challenging chirons, based on the regio- and stereoselective palladium(0) catalyzed reduction of 1-(1-alkenyl)cyclopropyl esters.[14]



(1*R*,2*S*)-**1** (de: 92%) (1*R*,2*S*)-**2** (2*S*)-**3** (de: 100 %)

a) Ph_3P=CH-R ; b) PPTS, MeOH; c) MsCl, NEt_3 ; d) HCOONa, Pd(0)

We had previously reported a convenient synthesis of asymmetric cyclopropanes,[3] such as (1*R*,2*S*)-2-methyl-1-(tetrahydropyranyloxy)cyclopropanecarbaldehyde **1** for example, from (2*S*)-dimethyl 2-methylsuccinate; this chiron and its enantiomer, being readily available either from enzymatic hydrolysis[15] or stereoselective alkylation of chiral imide enolates,[16] with high enantiomeric excesses (>95% ee). Wittig reaction of (1*R*,2*S*)-**1** with various alkylidenetriphenylphosphoranes then provided, after cleavage of the hydroxyl protective group, a Z,E mixture of (1*R*,2*S*)-2-methyl-1-(1-alkenyl)cyclopropanols **2**, in high yields (65–95%).[3,17] We have now investigated the reduction of the sulfonic acid ester derivatives of (1*R*,2*S*)-**2**, using sodium formate and *n*-butylzinc chloride as the hydride source,[14] in order to produce diastereomerically pure (2*S*)-alkylidene(2-methylcyclopropanes) **3**.

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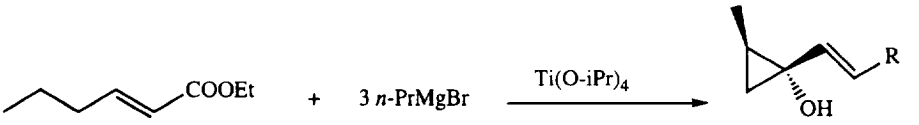


4 **5** **2'** (R = C_3H_7)

45 % (de = 100%)

For comparison we have prepared racemic *trans*-2-methyl-1(1-pentenyl)cyclopropanol **2'** (R=C_3H_7), diastereomerically pure in 45% yield, by treatment of the (E)-ethyl 2-hexenoate **4** with 3 equivalents of *n*-propylmagnesium bromide **5** in the presence of a catalytic amount (0.15 equiv) of titanium tetraisopropoxide in THF, following a recently reported procedure.[18]

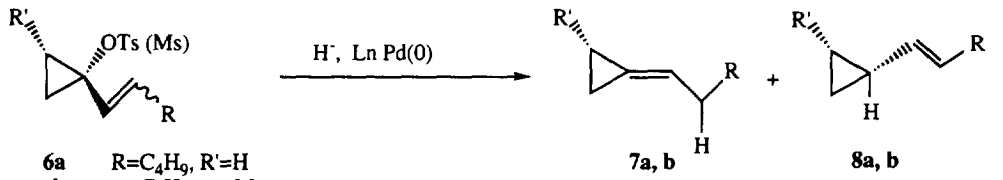
Mesylation (MsCl, NEt_3, Et_2O) of the (1*R*,2*S*)-2-methyl-1-(1-pentenyl)cyclopropanol **2** (R=C_3H_7) gave the corresponding sulfonate (85%),[19] which was submitted to palladium(0) catalyzed hydrogenolysis. We had previously reported that the regioselectivity of the palladium(0) catalyzed hydrogenolysis of 1-(1-alkenyl)cycloalkyl esters can be monitored by the nature of the hydride sources, by ring strain, silyl substitution of the allyl moities, charge transfer and frontier orbital controls, steric and electronic effects of trivalent phosphorus ligands.[14] Therefore, we have investigated the effect of substituents on the three-membered ring on the regioselectivity of this reduction.

We have shown that reaction of 1-(1-hexenyl)cyclopropyl tosylate **6a** (R=C_4H_9, R'=H) with sodium formate (3 equiv) in the presence of 10 mole% of [15]-crown-5-ether, catalyzed by palladium(0), formed from $Pd(dba)_2$ and diphenylphosphinoethane (dppe), provided in 81% yield a 50:50 mixture of regioisomeric reduction products **7a** and **8a** (see Table 1, entry 1). However, the same reaction performed in the presence of $Pd(dba)_2/PPh_3$, *i.e.*, using PPh_3 as Pd(0) ligand, led in 80% yield, exclusively to the hexylidenecyclopropane **7a** (entry 2).[14] Likewise hydrogenolysis of the mesylate (1*R*,2*S*)-**6b** (R=C_3H_7, R'=Me) by HCOONa and [15]-crown-5-ether, in the presence of $Pd(dba)_2$/dppe gave in 85% yield a 47:53 mixture of the (E)-(2*S*) pentylidene(2-methylcyclopropane) **7b** and of the (1*R*,2*S*)-2-methyl-1-(1-pentenyl)cyclopropane **8b** (entry 3). But as previously shown, use of more bulky palladium(0) ligands: PPh_3, P(p-anisyl)$_3$, P(o-anisyl)$_3$ and P(o-tolyl)$_3$, entailed the formation of **7b** as major product, thus increasing the ratio from 63 to 81% (entries 4–7).

The steric effect of trivalent phosphorus ligands is known to dominate the chemical behaviour of transition metal complexes.[20] It has been related to the apex angle Θ of a cylindrical cone centered at 2.28 Å from the center of the phosphorus atom, which touches the van der Waals radii of the outermost atoms of the ligands,[21] these angles have been correlated with a wide variety of phenomena including specificities in product formation.[22] The regioselectivity of the palladium(0) catalyzed hydrogenolysis reported in Table 1, appeared also greatly affected by the nature of the ligands. As previously observed for esters such as **6a**,[14] an increase of the size of the substituents on phosphorus increases the cone angle Θ and the bond lengths of palladium to phosphines, so decreasing their coordinating ability (reduction of the *s* character in the phosphorus cone pair) and therefore favoring coordination of the π-1,1-dimethyleneallyl moiety.[21] Indeed varying Θ from 145° (PPh_3) to 194° [P(o-tolyl)$_3$ or P(o-anisyl)$_3$] favoured the formation of the alkylidenecyclopropane **7b**, although this compound should be more strained than **8b**; effectively [$SE_{(methylenecyclopropane)} - SE_{(cyclopropane)} = 13.4$ kcal/mol].[23]

On the other hand, although treatment of the allylic ester **6a** by *n*-butylzinc chloride (from *n*-BuLi and $ZnCl_2$) as hydride source and in the presence of PPh_3 as Pd(0) ligand, led with a reverse regioselectivity to the vinylcyclopropane derivative **8a** exclusively (entry 8),[14] treatment of the cyclopropane ring methyl substituted allylic ester **6b** gave 38:64 and 14:86 mixtures of **7b** and **8b** when using dppe or PPh_3 as Pd(0) ligands, respectively (entries 9, 10). So under these conditions the hydrolysis appeared less regioselective.

Table 1. Palladium(0) catalyzed hydride reduction of 1-(1-alkenyl)cyclopropylsulfonates

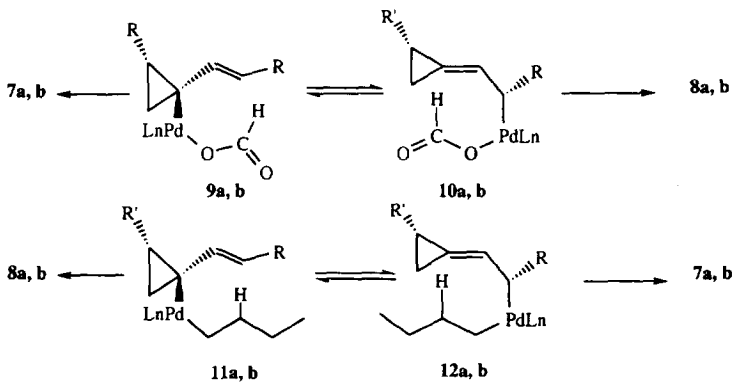


6a R=C_4H_9, R'=H
b C_3H_7 Me

7a, b **8a, b**

Entry		H⁻	Ln	Θ°	y%	ratio
1	R=C_4H_9, R'=H	HCOONa[a]	dppe	125	81	50:50[b]
2	-	-	PPh_3	145	80	100:0[b]
3	R=C_3H_7, R'=Me	-	dppe	125	85	47:53
4	-	-	PPh_3	145	80	63:37
5	-	-	P(p-anisyl)$_3$	145	81	69:31
6	-	-	P(o-anisyl)$_3$	194	79	77:23
7	-	-	P(o-tolyl)$_3$	194	83	81:19
8	R=C_4H_9, R'=H	*n*-BuZnCl	PPh_3	145	85	0:100[b]
9	R=C_3H_7, R'=Me	-	dppe	125	84	38:64
10	-	-	PPh_3	145	83	14:86

a) The hydrogenolysis was performed in the presence of 10 mole % of [15]-crown-5-ether; b) From ref. 14.



Unsymmetric π-allyl palladium complexes with the palladium situated closer to the cyclopropyl moiety and σ-complexes such as **9a** and **11a** have been considered to explain the high regioselectivity observed for the substitution of 1-(1-alkenyl)cyclopropyl sulfonates such as **6a**, either by soft or hard nucleophiles.[14] However, the presence of a 2-methyl group on the cyclopropane ring as on **6b** appeared to induce partial formation of the regioisomeric complexes **10b** and **12b**; this effect, which has been also observed when R is aromatic (*conjugation effect*),[14] can be therefore also overcome by using the steric effect of trivalent phosphorus palladium ligands. It must be underlined that while Pd(0) catalyzed substitution of 1-chloro-1-ethenyl-2-methylcyclopropane by dimethyl sodiosuccinate (*soft nucleophile*) gave a 4.7/1 mixture of (E) and (Z)-alkylidene(2-methylcyclopropanes),[24] on the other hand, Pd(0) catalyzed hydrogenolysis of **6b** by sodium formate gave diastereomerically pure (E)-**7b**, as determined from its ^1H and ^{13}C NMR data.[25] Fortunately regioisomeric compounds **7b** and **8b** were readily separable by preparative gas chromatography (SE 30, 80°C, nitrogen 1 bar). In conclusion this regioselective palladium(0) catalyzed hydrogenolysis offers not only an alternative to the Wittig reaction,[14] but opens a wide range of useful synthetic applications under current investigations. (*See the following communication*).

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25. (2*S*) Pentylidene(2-methylcyclopropane) **7b**: ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.62 (m, 1H), 0.93 (t, J=7 Hz, 1H), 1.13 (d, J=7Hz, 3H), 1.0–1.23 (m, 2H), 1.24–1.5 (m, 4H), 2.15 (m, 2H),

5.72(m, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 5.47, 13.97, 18.05, 18.22, 22.29, 31.35, 31.57, 117.42.87, 118.39.37; MS (EI) *m/z*: 124 (M^+, 0.23), 109 (9.95), 95 (100), 79 (17.61), 67 (55.9), 65 (7.33), 55 (25.06), 53 (17.61), 41 (34.46). (1*R*,2*S*) 2-Methyl-1-(1-pentenyl)cyclopropane **8b:** ^1H NMR ($CDCl_3$, 250 MHz) δ (ppm): 0.06 (m, 1H), 0.87–1.03 (m, 2H), 0.94 (t, J=7Hz, 3H), 1.03 (d, J=7Hz, 3H), 1.42(h, J=7Hz, 2H), 1.59 (m, 1H), 2.15(m, 2H), 5.06 (m, 1H), 5.45 (m, 1H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (ppm): 12.16, 13.80, 14.04, 14.36, 14.89, 22.93, 29.65, 129.30, 130.30; MS (EI) *m/z*: 124 (M^+, 22.09), 95 (80.12), 81 (43.56), 67 (100), 55 (22.78), 53 (17.11), 41 (33.80).

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