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REGIOSELECTIVE PALLADIUM(0) CATALYZED REDUCTION OF 1-ALKENYLCYCLOPROPYL ESTERS AS EQUIVALENT OF THE WITTIG REACTION§.

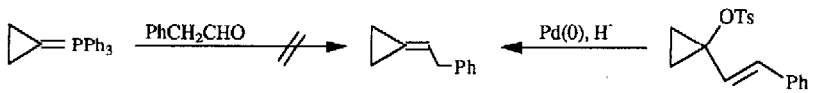
Jean Ollivier[a], Pier P. Piras[a], Andreas Stolle[a,b], Pierre Aufranc[a], Armin de Meijere[b,*] and Jacques Salaün[a,*]

Laboratoire des Carbocycles[a] (Associé au CNRS), Institut de Chimie Moléculaire d'Orsay, Bât. 420, Université de Paris-Sud, 91405 Orsay , France.
Institut für Organische Chemie der Georg-August Universität[b], D-3400 Göttingen, Germany.

Abstract: *Palladium(0) catalyzed reduction of 1-(1-alkenyl)- and 1-(1-cycloalkenyl)cyclopropyl esters provides an useful alternative to the Wittig reactions of cyclopropylidenetriphenylphosphorane or of cyclopropanone hemiacetals and an easy route to strained methylenecyclopropane derivatives.*

Cyclopropane derivatives provide building blocks of unprecedented synthetic potential (For recent reviews, see ref. 1-4). Specially strained alkylidenecyclopropanes[5] undergo either ring opening with palladium chloride to provide π-allyl palladium complexes which react with stabilized carbon nucleophiles[6], carbopalladation with vinyl- and arylhalides in the presence of Pd(0)[7], regioselective inter- and intramolecular Pd(0) catalyzed [3+2] cycloadditions with olefinic and acetylenic substrates[5,8], or Pauson Khand cyclizations in the presence of dicobalthexacarbonyl complexes of acetylenes[9].

Various types of methylenecyclopropane syntheses have recently emerged, but most of them are limited or involve multistep procedures with low overall yields. So, intramolecular reaction of vinylcarbenes is limited to methallyl- and ethallylchloride, dehydrochlorination of 1-chloro-1-methylcyclopropanes is limited to 1,1-dichloroethane as carbene source and to vicinally disubstituted alkenes, addition of carbenes or carbenoids to allenes results in formation of spiropentanes as main product, alkylation of lithiated methylene cyclopropanes provides only trimethylsilylated or α-hydroxyalkylated derivatives[5].

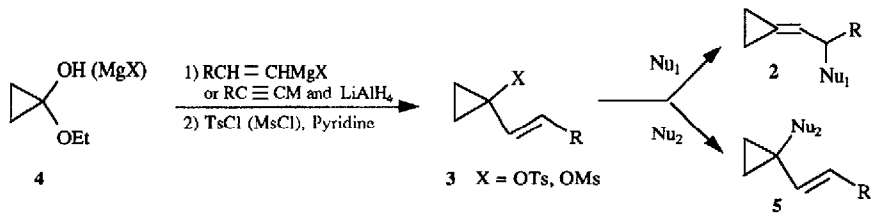


1 **2a** **3a**

Wittig olefination of aldehydes and ketones by cyclopropylidenetriphenylphosphorane **1** can lead to a wide range of alkylidenecyclopropanes with satisfactory yields[10], but the reaction does not occur when the carbonyl compound is readily enolizable. For instance, reaction of **1** with phenylacetaldehyde does not provide the expected phenylethylidenecyclopropane **2a**. We had previously claimed that Wittig reaction of the readily available cyclopropanone hemiacetal **4**[11] can provide an alternative to reaction of phosphorane **1**. However this olefination which requires the anchimeric assistance of an electron donating substituent on the ylides occurs only with arylidenetriphenylphosphoranes[12], triethylphosphonoacetate[12], or triphenyl phosphoranylideneacetates under benzoic acid catalysis[13].

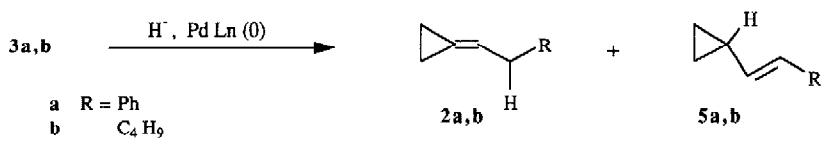
§ *Dedicated to Professor Michael Hanack on the occasion of his 60th birthday.*

We report now that palladium(0) catalyzed reduction of 1-(1-alkenyl)cyclopropyl esters **3** allows to overcome these problems. Effectively direct addition of ethenylmagnesium halides to **4** (or to its magnesium salt) or stepwise addition of alkynylorganometallic reagents (M = MgX, Li) followed by lithium aluminum hydride reduction, provided (*E*)-1-(1-alkenyl)cyclopropanols[14], which can be esterified by *p*-toluene- or methanesulfonyl chloride under standard conditions to provide sulfonates **3.**



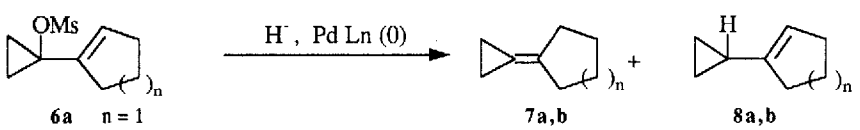
These 1,1-dimethyleneallyl esters undergo palladium(0) catalyzed substitution at the vinyl end by stabilized *(soft)* nucleophiles Nu_1 (enolates of malonic esters, β-dicarbonyl compounds, β-sulfonyl esters, Schiff bases, acetate and sulfonamide anions, ...) to provide methylenecyclopropanes **2** *exclusively* ; while tertiary substitution on the cyclopropane ring leading to 1-substituted ethenylcyclopropanes **5** occurs with non-stabilized *(hard)* nucleophiles Nu_2 (organometallic reagents, hydrides, azides, ...)[15].

Table I: ***Palladium catalyzed reduction products of 1-(1-alkenyl)cyclopropyl sulfonates 3a,b***



Entry	*R*	*H⁻*	*Ln*	*Y %*	*(ratio)*
1	Ph	*n*-BuZnCl	PPh_3	93	(0:100)
2	-	HCOOH, NEt_3	PBu_3	96	(0:100)
3	-	HCOONa	dppe	46	(42:58)
4	-	HCOONa, 15-C-5	dppe	90	(37:63)
5	-	HCOONa, 15-C-5	PPh_3	95	(62:38)
6	-	HCOONa, 15-C-5	P(o-tolyl)3	94	(85:15)
7	-	HCOONa, 15-C-5	P(o-anisyl)3	91	(90:10)
8	C_4H_9	*n*-BuZnCl	PPh_3	85	(0:100)
9	-	HCOONa, 15-C-5	dppe	81	(50:50)
10	-	HCOONa, 15-C-5	PPh_3	80	(100:0)

Table II: ***Palladium catalyzed reduction products of 1-(1-cycloalkenyl)cyclopropyl sulfonates 6a,b.***

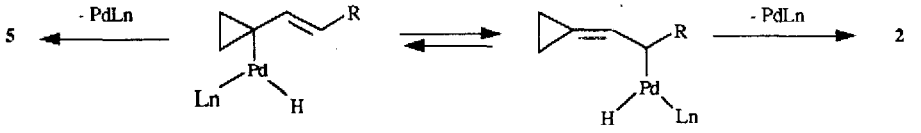


11 (n=1)	*n*-BuZnCl	PPh_3	83	(0:100)
12 (n=1)	HCOONa, 15-C-5	PPh_3	80	(98:2)
13 (n=2)	HCOONa, 15-C-5	PPh_3	85	(98:2)

We disclose here that reduction products of 1-(1-alkenyl)cyclopropyl esters **3** are highly depending on the hydride sources (H^-) and the ligands (Ln) of palladium(0). Thus reaction of 1-styrylcyclopropyl tosylate **3a** with *n*-butylzinc chloride (from *n*-BuLi and $ZnCl_2$) in the presence of palladium dibenzylideneacetone [$Pd(dba)_2$] and triphenylphosphine (PPh_3), a system known to perform hydrogenolysis by attack of hydride (*from β-elimination*) at the less substituted site of π-allyl palladium complexes[16], yields the styrylcyclopropane **5a**[17], favored by conjugation, *exclusively* (see Table I, entry 1) ; on the same way treatment of **3a** with formic acid and triethylamine using $Pd(dba)_2$ and tri-*n*-butylphosphine (PBu_3), a system known however to induce reduction with *reverse* regioselectivity, *i.e.*, by attack of hydride at the more substituted site of π-allyl palladium intermediates[18], produces also **5a** (entry 2). On the other hand, reaction of **3a** with sodium formate (3 equiv) in the presence of $Pd(dba)_2$ and diphenylphosphinoethane (dppe) gives a 42:58 mixture of isomeric cyclopropane derivatives **2a**, evidenced by a single vinylic proton in ^1H NMR at δ 5.95 [15], and **5a** (entry 3), whose yields are improved from 46 to 90% (ratio 37:63) on simple addition of 10 mole % [15]-crown-5 ether (entry 4). Sodium formate, [15]-crown-5 ether and $Pd(dba)_2/PPh_3$ as catalyst favors the methylenecyclopropane **2a** (ratio **2a**:**5a** = 62:38, entry 5). Moreover used of more bulky palladium ligands, *i.e.*, tri o-tolylphosphine [P(*o*-tolyl)$_3$] and tri *o*-anisylphosphine [P(*o*-anisyl)$_3$], leads to the formation of **2a** as major reduction product (ratio 85:15 and 90:10, respectively, entries 6,7).

Likewise reaction of 1-(1-hexenyl)cyclopropyl tosylate **3b** with n-BuZnCl in the presence of $Pd(dba)_2/PPh_3$ yields (1-hexenyl)cyclopropane **5b**[19], *exclusively*, (entry 8); but reaction with sodium formate and [15]-crown-5 ether in the presence of $Pd(dba)_2$/dppe provides a 50:50 mixture of reduction products **5b** and **2b**[20] (81%, entry 9). In this case, no conjugative effect as above has to be overcome, so PPh_3 appears sufficientyl bulky to induce formation of the hexylidenecyclopropane **2b**, *exclusively*, in 80% yield (entry 10).

Reaction of 1-(1-cyclopentenyl)cyclopropyl mesylate **6a** (n = 1) (from addition of 1-cyclopentenyl lithium to **4** followed by mesylation) with *n*-BuZnCl, $Pd(dba)_2/PPh_3$ gives 1-(1-cyclopentenyl)cyclopropane **8a**[21], *exclusively*, (83%, Table II, entry 11); with HCOONa, 15-crown-5 ether, $Pd(dba)_2/PPh_3$ a 98:2 mixture of cyclopentylidenecyclopropane **7a** (n = 1)[22] and **8a** is obtained in 80% yield (entry 12). Similar results are obtained from 1-(1-cyclohexenyl)cyclopropyl mesylate **6b** (n=2), (entry 13).



9 **10**

Formation of an unsymmetric π–complex where the palladium would be situated closer to the cyclopropyl moiety has been suggested to explain the unexpectedly *high selectivity* observed for substitution of 1-(1-ethenyl)cyclopropyl sulfonates **3** (R = H) by stabilized nucleophiles at the primary vinylic end[15]. It appears clearly now that bulky catalyst ligands such as PPh_3, P(*o*-tolyl)$_3$, P(*o*-anisyl)$_3$,..can favor, after hydride attack of the palladium (by H^- or $HCOO^-$ followed by decarboxylation), formation of σ–complexes **10** which lead, after reductive elimination of PdL_n, to strained methylenecyclopropanes **2** and therefore limit formation of σ–complexes **9**, supposed to provide, after PdLn elimination, conjugated cyclopropanes **5**.

In conclusion, by using suitable hydride sources and ligands it is therefore possible to obtain methylenecyclopropane derivatives in high yields from the palladium(0) catalyzed reduction of readily available

1-(1-alkenyl)- and 1-(1-cycloalkenyl)cyclopropyl sulfonates. This reaction offers not only **an alternative to the Wittig reaction** of cyclopropylidenetriphenylphosphorane **1**[10] but moreover allows to overcome the limitations met in the Wittig reactions of cyclopropanone hemiacetal **4**[12]. As chiral derivatives of substrates **3** are now available with high enantiomeric excesses[3], this regioselective reduction opens a wide range of useful synthetic applications under current investigations.

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19) ^{1}H NMR(250 MHz): 0.27-0.33(m, 2H), 0.61-0.68(m, 2H), 0.9(t, 3H, J=7Hz), 1.2-1.4(m, 5H), 1.92-2.06(m, 2H), 4.96(dd, 1H, J=15.2 and 8.5 Hz), 5.51 (dt, 1H, J = 15.2 and 6.8 Hz); IR($CDCl_3$) 1665 cm^{-1}; MS m/z 124 ($M^{+\cdot}$ 28), 68(100).

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