

Palladium Catalysts for the Formylation of Vinyl Triflates To Form α,β -Unsaturated Aldehydes**

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Dedicated to Professor G. Oehme on the occasion of his 70th birthday

An essential challenge for modern organic chemistry is the efficient and direct synthesis of important functional groups without the need for protection/deprotection steps, functional-group interconversions, and harsh reaction conditions. In this respect, α,β -unsaturated aldehydes constitute particularly interesting targets. On the one hand, they have found numerous applications as building blocks for the synthesis of various biologically active compounds,^[1,2] polymers,^[3] fragrances,^[4] feed additives,^[5] and other compounds. On the other hand, there is a need for improved and generally applicable synthetic routes to these important building blocks.^[6] α,β -Unsaturated aldehydes are typically prepared by oxidation of the corresponding allylic alcohols,^[7] Horner–Wadsworth–Emmons^[8] and Peterson^[9] olefinations, aldol condensation, and Mannich reaction.^[6,10,11]

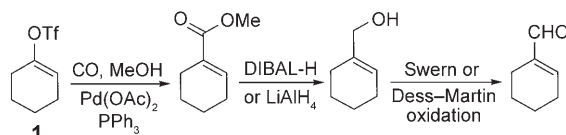
In recent years, the transformation of vinyl triflates into α,β -unsaturated aldehydes has become an important reaction that is widely used in the synthesis of various natural products. In general, this transformation is carried out in three steps, through palladium-catalyzed alkoxycarbonylation followed by reduction with DIBAL-H or LiAlH_4 and subsequent oxidation of the resulting alcohol to the aldehyde (Scheme 1).^[1] A more straightforward and atom-economical

(CO/H_2), is not known.^[16] Previously described palladium-catalyzed formylation reactions require relatively high catalyst loadings (in general 10 mol %) and the use of an additive (LiCl).

Herein, we describe the first palladium-catalyzed synthesis of α,β -unsaturated aldehydes from vinyl triflates that makes use of synthesis gas. Recently, we developed a novel palladium-catalyzed reductive carbonylation of aryl and heteroaryl halides with $\text{Pd}(\text{OAc})_2/\text{cataCXium A}$ (di(1-adamantyl)-*n*-butylphosphine) as the catalyst system.^[17,18] This method enabled the first hydroformylation of aryl halides to be performed on an industrial scale (> 1000 kg). On the basis of these studies, we extended the scope of the reductive formylation with synthesis gas to vinyl bromides.^[19] However, from a synthetic point of view, vinyl triflates are more convenient and versatile substrates, as they can be prepared readily from a variety of ketones.^[20] In this regard, the use of vinyl triflates as substrates for formylation reactions is appealing.

To find a suitable palladium catalyst and establish optimal reaction conditions, we studied the reductive carbonylation of cyclohex-1-en-1-yl triflate (**1**) as a model system. Initially, different phosphine and carbene ligands were tested. Catalytic experiments were carried out in the presence of $\text{Pd}(\text{OAc})_2$ (1.5 mol %) and the corresponding monodentate ligand (4.5 mol %) or bidentate ligand (2.25 mol %) in DMF at 60–100 °C and 20 bar of CO/H_2 (1:1). Selected results are summarized in Table 1. Unfortunately, cataCXium A, which is an excellent ligand for the reductive carbonylation of aryl and vinyl halides, gave only a trace amount of the desired product (Table 1, entry 1). Instead, cyclohex-1-ene-1-carboxylic anhydride was formed as the major product.^[21] All other monodentate ligands tested in this reaction were equally inefficient (Table 1, entries 2–4).

As bidentate ligands have been employed successfully in the past in palladium-catalyzed carbonylation reactions,^[22,23] we tested a number of chelating phosphines (Table 1, entries 5–16). The use of bidentate ligands with diphenylphosphino substituents led to an increase in the yield of the cyclohexenecarbaldehyde to up to 21 %. However, the best results were observed when diphosphine ligands with bulky alkyl substituents were used (Table 1, entries 13–16). To explore more thoroughly the potential of bulky bidentate phosphine ligands in the model reaction, we also synthesized new chelating ligands with di-1-adamantylphosphino moieties attached to various backbones (Scheme 2). There were two reasons for our decision to use adamantyl substituents: First, the adamantyl group is a very bulky substituent, even more

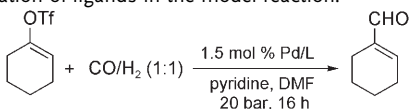


Scheme 1. Typical synthesis of an α,β -unsaturated aldehyde from a vinyl triflate. Tf = trifluoromethanesulfonyl.

approach to α,β -unsaturated aldehydes is the one-step reductive carbonylation of vinyl triflates. Although the use of tin^[12,13] and silyl^[14,15] hydrides has been described, to the best of our knowledge reductive formylation with the simplest and most environmentally benign formyl source, synthesis gas

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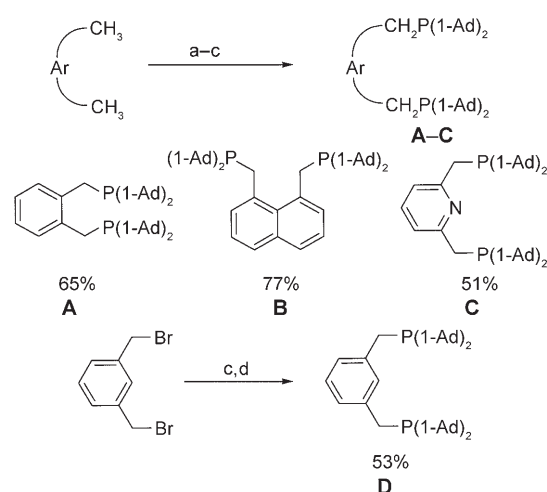
Table 1: Variation of ligands in the model reaction.^[a]


Entry	Ligand ^[b]	T [°C]	Conversion [%] ^[c]	Yield [%] ^[c]
1	cataCXium A	80	100	4
2	PPh ₃	100	98	1
3	IPr ₂ -HCl	100	90	2
4	IMes-HCl	100	94	3
5	dppf	80	100	14
6	dppe	80	61	18
7	dppp	80	60	21
8	dppb	80	81	11
9	diop	80	100	7
10	binap	80	40	5
11	xantphos	80	99	0
12	dppx	80	91	12
13	dtbpx ^[e]	80	100	74
14	josphos	60	50	29
15	josphos	80	100	73
16	josphos	100	100	65
17	A	60	34	27
18	A	80	100	85
19	A	100	100	67
20	B	80	100	0
21	C	80	5	0

[a] Reaction conditions: Vinyl triflate (0.5 mmol), pyridine (0.75 mmol), diglyme (0.35 mmol; internal standard for GC), Pd(OAc)₂ (1.5 mol%), monodentate (4.5 mol%) or bidentate ligand (2.25 mol%), DMF (2 mL), CO/H₂ (1:1; 20 bar), 60–100°C, 16 h. [b] IPr₂-HCl = 1,3-diisopropyl-4,5-dihydroimidazolium chloride, IMes-HCl = 1,3-bis(2,4,6-trimethylphenyl)imidazolium chloride, dppf = 1,1'-bis(diphenylphosphino)ferrocene, dppe = 1,2-bis(diphenylphosphino)ethane, dppp = 1,3-bis(diphenylphosphino)propane, dppb = 1,4-bis(diphenylphosphino)butane, diop = O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane, binap = 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, dppx = α,α'-bis(diphenylphosphino)-o-xylene, dtbpx = α,α'-bis(di-*tert*-butylphosphino)-o-xylene, josphos = 1-[2-(diphenylphosphino)ferrocenyl]ethylidicyclohexylphosphine. [c] Yield and conversion were determined by GC. DMF = N,N-dimethylformamide.

sterically hindered than the *tert*-butyl group, and second, phosphines containing two adamantyl groups are air-stable solids which can be handled conveniently and even exposed to air for a short period of time.^[24] The new ligands **A–C** were prepared in a one-pot procedure that involved the α metalation of a dimethylarene and subsequent treatment with Ad₂PCl.^[25] The resulting phosphines precipitated directly from the reaction mixture and were isolated readily by filtration after quenching the reaction mixture with water. For the synthesis of ligand **D**, Ad₂PH was alkylated with α,α'-dibromo-*meta*-xylene followed by treatment with a base.^[26]

Interestingly, pronounced differences were observed in the formylation reaction with the novel ligands, in terms of both efficiency and selectivity. The use of the *meta*-xylene-related ligands **C** and **D** resulted in very low conversion (<5%), whereas complete conversion was observed with ligand **B**; however, none of the desired aldehyde was detected. In sharp contrast to the reactions with ligands **B** and **C**, the reaction with ligand **A**, which has an *ortho*-xylene



Scheme 2. Synthesis of novel bidentate phosphines: a) *n*BuLi, TMEDA, *t*BuONa, heptane, 65°C, 1 h (for **A**, **B**); *n*BuLi, TMEDA, Et₂O, room temperature, 16 h (for **C**); b) (1-Ad)₂PCl in THF, –30°C, 20 min, then room temperature, 12 h; c) (1-Ad)₂PH, EtOH, 80°C, 30 min; e) Et₃N, room temperature, 16 h. Ad = adamantyl, TMEDA = *N,N,N',N'*-tetramethylethylenediamine.

backbone, afforded the desired aldehyde in 85% yield (Table 1, entry 18). Comparison of the efficiency of ligand **A** with that of its known *tert*-butyl analogue dtbpx and josphos reveals a distinct advantage of ligand **A** (Table 1, entries 13 and 18, 15 and 18, respectively). To further optimize the reaction conditions, we also studied the effect of the reaction temperature. Optimal yields were observed when the reactions were carried out at 80°C (Table 1, entries 14–19). At a lower temperature, conversion was incomplete, and at 100°C the yields decreased, presumably as a result of decomposition of the starting material. We studied the effect of different bases on the reaction with a combination of Pd(OAc)₂ and ligand **A** as the precatalyst at 80°C. Pyridine was found to be the most efficient base, whereas the use of TMEDA, NEt₃, and NEt₃Pr₂ led to lower yields, and the inorganic base potassium carbonate was inactive.

Next, different vinyl triflates were formylated with synthesis gas under the optimized conditions (Table 2). The reaction was applied successfully to cycloalkenyl triflates with six-, seven-, and eight-membered rings (Table 2, entries 1–3). These nonfunctionalized triflates were converted smoothly into the corresponding aldehydes in high yields (85–87%). In contrast, the reaction of cyclopent-1-en-1-yl triflate gave the desired product in low yield. An analogous five-membered-ring triflate was also found to be a poor substrate for Bu₃SnH-mediated formylation.^[13]

As the introduction of a formyl group into six-membered-ring compounds is of considerable importance in organic synthesis,^[1,15] we focused our attention on the reactions of cyclohexenyl triflates with substituents at various positions. Derivatives of cyclohexenyl triflate with substituents at the 4-position also underwent formylation readily to give the corresponding aldehydes in high yields (Table 2, entries 4 and 5). However, the *cis*-3,5-disubstituted cyclohexenyl triflate **6** is somewhat less reactive (Table 2, entry 6). The sterically encumbered substrates **7–9** were also converted into

Table 2: Scope and limitations of the formylation of vinyl triflates with synthesis gas.^[a]

$\text{Vinyl triflate} + \text{CO/H}_2 (1:1) \xrightarrow[\text{pyridine, DMF, 80–120 } ^\circ\text{C, 20 bar, 16 h}]{\text{Pd(OAc)}_2 (1.5 \text{ mol } \%), \text{A} (2.25 \text{ mol } \%)}$					$\text{Vinyl triflate} \rightarrow \text{Vinyl aldehyde}$				
Entry	Vinyl triflate	T [°C]	Conversion [%] ^[b]	Yield [%] ^[b]	Entry	Vinyl triflate	T [°C]	Conversion [%] ^[b]	Yield [%] ^[b]
1		80	100	85	8		80	100	63
2		80	100	87	9		80	92	63 ^[c]
3		80	100	85	10		120	98	42 ^[d]
4		80	100	87	11		80	100	69 ^[e]
5		80	99	72	12		80	100	trace
6		80	95	57	13		80	100	51 ^[c]
7		80	97	61					

[a] Reaction conditions: Vinyl triflate (0.5 mmol), pyridine (0.75 mmol), diglyme (0.35 mmol; internal standard for GC), Pd(OAc)₂ (1.5 mol %), ligand **A** (2.25 mol %), DMF (2 mL), CO/H₂ (1:1; 20 bar), 80 or 120 °C, 16 h. [b] Yields and conversions were determined by GC. [c] The response factor of the starting triflate was used to calculate the yield. [d] Reaction time: 8 h. [e] Yield of the isolated product.

the corresponding aldehydes (Table 2, entries 7–9). The same was true for the bulky spiro compound **10**, although in this case a higher temperature (120 °C) was required for full conversion (Table 2, entry 10). The formylation procedure can be applied to even more complex substrates, such as cholest-3-en-3-yl triflate (**11**; Table 2, entry 11). The triflate **11** reacted under standard conditions to afford the corresponding unsaturated aldehyde in 69 % yield. As the application of heterocyclic triflates as coupling partners in palladium-catalyzed reactions is scarcely described in literature,^[27] we also tested the two heterocyclic triflates **12** and **13** in the formylation reaction. Whereas the reaction of the nitrogen-containing substrate **12** gave only a trace amount of the desired aldehyde, that of the corresponding dihydropyranyl substrate **13** afforded the product in 51 % yield (Table 2, entries 12 and 13).

In summary, we have described the palladium-catalyzed formylation of cyclic vinyl triflates with synthesis gas. A novel catalytic system comprising the bidentate ligand **A** enables the efficient transformation of various six-, seven-, and eight-membered-ring triflates into the corresponding α,β -unsaturated aldehydes. This method can be used to introduce a formyl group into derivatives of elaborate natural compounds, as illustrated by the formylation of (+)-cholest-3-en-3-yl triflate. The novel bidentate ligands should also be useful for a variety of other coupling reactions.

Experimental Section

Triflates^[28] and di(1-adamantyl)chlorophosphine^[29] were prepared according to literature procedures.

Synthesis of **A**: *t*BuONa (575 mg, 6 mmol) and a magnetic stir bar were placed in a 50 mL Schlenk flask, which was then sealed with a septum cap, evacuated, and filled with argon. Heptane (6 mL), TMEDA (0.91 mL, 747 mg, 6.4 mmol), and *ortho*-xylene (245 μ L, 212 mg, 2 mmol) were added to the flask with syringes. A solution of *n*BuLi (2.5 M in hexanes; 2.4 mL, 6 mmol) was then added dropwise with stirring, and the reaction mixture was heated at 65 °C for 1 h and then cooled to room temperature. A red precipitate was filtered, washed with heptane (3 $\times$ 3 mL), and suspended in heptane (11 mL). The reaction flask was cooled to –30 °C, and a solution of di(1-adamantyl)chlorophosphine (1.42 g, 4.2 mmol) in THF (8 mL) was added dropwise over 10 min. The reaction mixture was then allowed to warm to room temperature and was stirred overnight. The mixture was quenched with degassed distilled water (10 mL), and the resulting precipitate was filtered and washed with water (2 $\times$ 6 mL) and methanol (3 $\times$ 8 mL) to give crude **A** (1.05 g, 74 %) as an off-white solid. The crude compound was of high purity according to NMR spectroscopy, but contained a tiny amount of an insoluble material. It was purified by precipitation with methanol from a saturated solution in dichloromethane to give **A** (0.93 g, 65 %) as white crystals. M.p.: 229–230 °C; ¹H NMR (300 MHz, CDCl₃, 24 °C): δ = 7.62–7.49 (m, 2H, C_{Ar}–H), 7.10–6.98 (m, 2H, C_{Ar}–H), 3.00 (d, ²J_{P,H} = 3.3 Hz, 4H, CH₂), 2.03–1.61 ppm (m, 60H, 1-Ad); ¹³C{¹H} NMR (75 MHz, CDCl₃, 24 °C): δ = 139.3 (dd, *J*_{P,C} = 3.0, 10.9 Hz, C_{quat}), 130.9 (d, *J*_{P,C} = 16.4 Hz, CH), 124.9 (d, *J*_{P,C} = 1.9 Hz, CH), 41.0 (d, *J*_{P,C} = 10.5 Hz, CH₂), 37.0 (CH₂), 36.8 (d, *J*_{P,C} = 23.3 Hz, C_{quat}), 28.7 (d, *J*_{P,C} = 7.8 Hz,

CH), 21.8 ppm (dd, $J_{\text{PC}} = 3.8, 22.9$ Hz, CH_2); $^{31}\text{P}\{^1\text{H}\}$ NMR (121 MHz, CDCl_3 , 24°C): $\delta = 26.2$ ppm; HRMS (EI): m/z calcd for $\text{C}_{48}\text{H}_{68}\text{P}_2$: 706.47908 [M^+]; found: 706.476976; elemental analysis: calcd (%) for $\text{C}_{48}\text{H}_{68}\text{P}_2$: C 81.54, H 9.69; found: C 81.09, H 9.55.

Synthesis of (+)-cholest-3-en-3-carbaldehyde: The reaction was carried out in a Parr Instruments 4560 series 300 mL autoclave containing an alloy plate with wells for four 4 mL glass vials. Ligand **A** (7.95 mg, 1.12×10^{-2} mmol, 2.25 mol %), **11** (259.4 mg, 0.5 mmol), and a magnetic stir bar were placed in each of the vials, which were then capped with a septum equipped with an inlet needle and flushed with argon. A stock solution (2.1 mL) prepared from $\text{Pd}(\text{OAc})_2$ (10.2 mg, 1.5 mol %), pyridine (362 μL , 4.5 mmol), and DMF (12 mL) was added to each vial with a syringe. The vials were placed in an alloy plate, which was then placed in the autoclave. Once sealed, the autoclave was purged several times with synthesis gas, then pressurized to 20 bar at room temperature and heated at 80°C for 16 h. It was then cooled to room temperature and vented to discharge the excess synthesis gas. The contents of the vials were combined, water (40 mL) was added, and the product was extracted with diethyl ether (3×30 mL). The extracts in diethyl ether were washed with brine, dried over Na_2SO_4 , and evaporated with adsorption onto silica gel. The crude product was purified by column chromatography (eluent: heptane) to give the title compound (550 mg, 69%) as a white solid. M.p.: 78°C ; ^1H NMR (300 MHz, CDCl_3 , 24°C): $\delta = 9.41$ (s, 1H, CHO), 6.41–6.45 (m, 1H, C=CH), 2.45–0.80 (m, 40H), 0.72 (s, 3H, CH_3), 0.67 ppm (s, 3H, CH_3); $^{13}\text{C}\{^1\text{H}\}$ NMR (75 MHz, CDCl_3 , 24°C): $\delta = 194.4$ (C=O), 155.6 (CH=), 139.7 (C=), 56.4, 56.3, 53.3, 47.6, 35.8, 35.5, 28.1, 22.9, 22.6, 18.7, 12.5, 12.2 (12 CH and CH_3), 40.0, 39.6, 36.2, 33.1, 32.1, 28.3, 26.8, 24.2, 23.9, 21.3, 19.5 (11 CH_2), 42.7, 35.8 ppm (2 C_{quat}); IR (attenuated total reflection, neat): $\tilde{\nu} = 2942$ (m), 1686 (vs, C=O), 1644 (w), 1462 (w), 1383 (w), 1190 (w), 1069 (w), 992 (w), 958 (w), 931 (w), 907 (w), 869 (w), 784 (w), 717 cm^{-1} (w); MS (70 eV): m/z (%): 398 (100) [M^+], 383 (48) [$M-\text{CH}_3$] $^+$, 369 (26) [$M-\text{CHO}$] $^+$, 355 (9), 328 (15), 315 (15), 285 (33), 272 (34); elemental analysis: calcd (%) for $\text{C}_{28}\text{H}_{46}\text{O}$: C 84.36, H 11.63; found: C 84.42, H 11.46.

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