

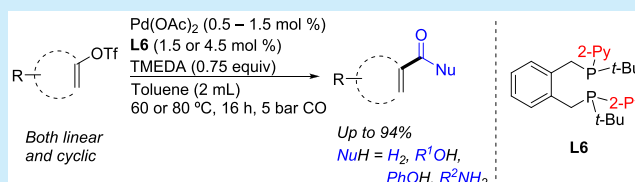
Pd-Catalyzed Carbonylation of Vinyl Triflates To Afford α,β -Unsaturated Aldehydes, Esters, and Amides under Mild Conditions

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S Supporting Information

ABSTRACT: An efficient and general protocol for the synthesis of α,β -unsaturated aldehydes, esters, and amides via carbonylation of vinyl triflates including derivatives of camphor, ketoisophorone, verbenone, and pulegone was developed. Crucial for these transformations is the use of a specific palladium catalyst containing a pyridyl-substituted dtbpx-type ligand. This procedure also allows for an easy access of dicarbonylated products from the corresponding ketones.

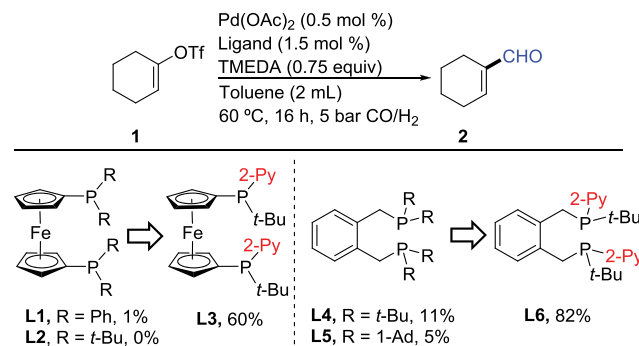


Continuing to attract the interests of researchers from academia and industry, α,β -unsaturated carbonyl compounds, especially aldehydes, constitute versatile building blocks for organic synthesis.¹ In recent years, they have been used more specifically for the synthesis of biologically² and optically³ active compounds, agrochemicals,⁴ pharmaceuticals,⁵ fullerene-based materials,⁶ flavors,⁷ natural compounds,⁸ polymers,⁹ fragrances,¹⁰ and many more. Traditionally, α,β -unsaturated aldehydes were produced by oxidation of the corresponding allylic alcohols,¹¹ Horner–Wadsworth–Emmons¹² and Peterson¹³ olefinations, aldol condensations,¹⁴ and Mannich reactions.¹⁵ Furthermore, dehydrogenation of corresponding saturated aldehydes,¹⁶ hydroformylation of alkynes¹⁷ or vinyl bromides,¹⁸ and other methods¹⁹ have also been described. Nevertheless, there is a need for improved and generally applicable synthetic routes to these important building blocks starting from easily available substrates. In this respect, ketones are “ideal” candidates, which can be readily transformed into more reactive vinyl triflates²⁰ and related compounds. In the 1990s, the transformation of vinyl triflates to α,β -unsaturated aldehydes was first described as a three step reaction.²¹ Later on, a more straightforward and atom-economical approach—the reductive carbonylation of vinyl triflates—was disclosed using silyl hydrides.²² Obviously, the use of synthesis gas (CO/H₂), which is the simplest and most environmentally benign formyl source, is more appealing. In this respect, we described the first palladium-catalyzed formylations of vinyl triflates.²³ However, a comparably high temperature (80–120 °C), pressure (20 bar), and catalyst loading (1.5 mol % Pd) were necessary for successful transformations, and the procedure was limited to cyclic substrates. To improve this versatile methodology, the applied ligand is of crucial importance. In recent years, we introduced a series of pyridyl-substituted phosphine ligands for various types of carbonylation reactions.²⁴ Here, the pyridyl nitrogen atom actively participates in the activation of the cosubstrate such as alcohols, amines, etc. Thus, we had the idea that such ligands might also improve the heterolytic activation of hydrogen in

synthesis gas. On the basis of this assumption, herein, we present a general palladium-catalyzed carbonylation of vinyl triflates to afford not only α,β -unsaturated aldehydes but also esters and amides under very mild conditions.

At the start of this project, we studied the reductive carbonylation of cyclohexenyl triflate (**1**) as the benchmark reaction. Compared to previous carbonylations of aryl and vinyl triflates, various phosphine ligands were compared under significantly milder conditions [0.5 mol % Pd(OAc)₂, 0.75 equiv of tetramethylethylenediamine (TMEDA), 5 bar CO/H₂, 60 °C]. As shown in Scheme 1, previously known ligands for this transformation such as dppf **L1**, dtbpf **L2**, dtbpx **L4**, and dadpx **L5** gave only low yields of the desired α,β -unsaturated aldehyde **2**, while decomposition of the substrate was mainly observed.

Scheme 1. Pd-Catalyzed Synthesis of Cyclohex-1-enecarbaldehyde in the Presence of Different Ligands^a



^aReaction conditions: 0.5 mmol of **1**, Ar. Yields and conversions were determined by GC with *n*-hexadecane as standard; the values given refer to the yields of **2**.

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However, following the proposal of *vide supra* replacement of the phenyl or *t*-butyl group on both ligand scaffolds by 2-pyridyl (L3 and L6), the desired transformation took place, and **2** was obtained in good to very good yields (60% and 82%, respectively). Testing other standard mono- and bidentate phosphines as well as specifically available ones from our laboratory gave no positive results at all (see the SI, Scheme S1). Notably, in some cases (L1 and L4), high conversion was observed, and cyclohex-1-ene-1-carboxylic anhydride was detected as a major side-product.

Further optimization of the Pd(OAc)₂/L6 system revealed a strong influence of base, ligand concentration, and temperature (Table 1). As expected, a control experiment without any

Table 1. Pd-Catalyzed Synthesis of Cyclohex-1-enecarbaldehyde under Various Conditions^a

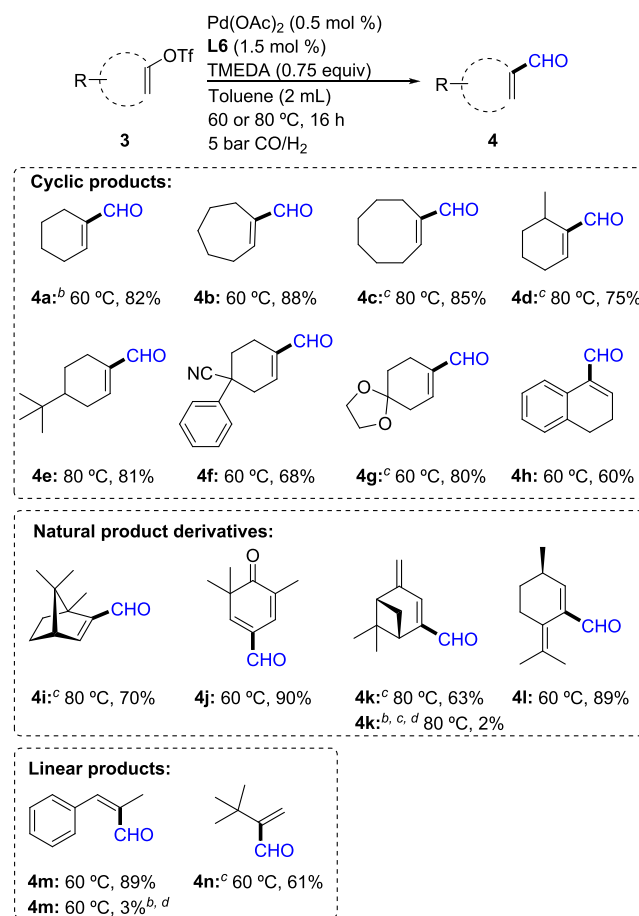
entry	Pd(OAc) ₂ (L6)/mol %	base ^b	solvent	conversion (yield)/%
1	0 (0)	TMEDA	toluene	3 (0)
2	0.5 (0.75)	TMEDA	toluene	38 (5)
3	0.5 (1.5)	TMEDA	toluene	100 (82)
4 ^c	0.5 (1.5)	TMEDA	toluene	54 (44)
5	0.5 (1.5)	NaOtBu	toluene	52 (0)
6	0.5 (1.5)	Na ₂ CO ₃	toluene	20 (2)
7	0.5 (1.5)	none	toluene	9 (1)
8	0.5 (1.5)	TMEDA	THF	100 (76)
9	0.5 (1.5)	TMEDA	DMF	100 (88)
10	0.5 (1.5)	TMEDA	DMSO	100 (24)

^aReaction conditions: 0.5 mmol of **1**, Ar. Yields and conversions were determined by GC with *n*-hexadecane as standard. ^b0.75 equiv for TMEDA; 1.5 equiv for other bases. ^cReaction performed at 40 °C.

catalyst revealed basically no conversion (3%) of **1** and no product formation (Table 1, entry 1), while under optimal conditions full conversion was observed, and 88% of the product could be obtained (Table 1, entry 9). Apart from toluene, the reaction also proceeded smoothly in tetrahydrofuran (THF) and dimethylformamide (DMF) (Table 1, entries 8 and 9).

With the optimized reaction conditions in hand, the formylation of structurally diverse vinyl triflates with synthesis gas was tested (Scheme 2). In addition to cyclohexenyl triflate, 13 other substrates were converted to the corresponding products in good to excellent yields. Vinyl triflates of a six- and seven-membered ring were formylated successfully under optimized conditions (**4a** and **4b**). For the eight-membered ring triflate, a higher temperature (80 °C) and catalyst loading were necessary to give **4c** in 85% isolated yield. Furthermore, derivatives of cyclohexenyl triflate with substituents at various positions underwent formylation smoothly to give the corresponding aldehydes in 60–81% isolated yields (**4d–4h**). With regard to the functionalization of naturally occurring terpenes, it is interesting that derivatives of camphor, ketoisophorone, verbenone, and pulegone can be easily converted to the corresponding aldehydes at 60 or 80 °C in high yields (**4i–4l**). Notably, this protocol is also applicable to

Scheme 2. Substrate Scope of the Pd-Catalyzed Synthesis of α,β -Unsaturated Aldehydes^a



^aReaction conditions: 0.5 mmol of **3**, Ar. Yields of isolated products. ^bGC yield. ^c1.5 mol % Pd(OAc)₂, 4.5 mol % L6. ^dL5 was used instead of L6.

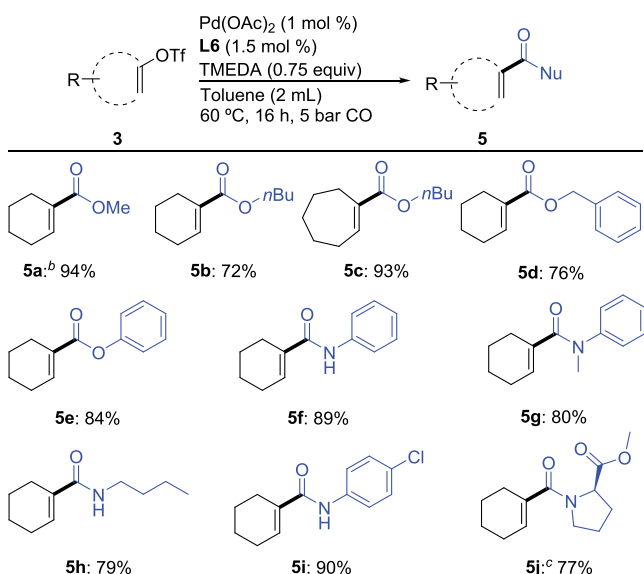
the formylation of linear vinyl triflates (**4m** and **4n**), which are described here to the best of our knowledge for the first time. To further demonstrate the superiority of the 2-pyridyl-substituted ligand, control experiments were made in the presence of the previous state-of-the-art ligand L5. However, **4k** and **4m** were detected in <3% yield by GC.

To understand the improved performance of this specific palladium catalyst system and to get further insights, *in situ* ³¹P NMR spectroscopic measurements were performed. After mixing cyclopentadienyl allyl palladium with L6 and **3a** in *d*8-toluene at 60 °C, the parent ligand ($\delta = 8.8$ ppm) immediately disappeared, and three other phosphorus species were mainly detected ($\delta = 19.73, 34.56, \text{ and } 52.28$ ppm, ratio of 1:2.8:1.1) (see the SI). On the basis of a similar characterized reference complex [L6Pd- η^3 -allyl]OTf,^{24d} we assign the largest signal at 34.56 ppm to the oxidative addition product [L6Pd- η^3 -cyclohexenyl]OTf. In contrast, stirring cyclopentadienyl allyl palladium with L4 instead of L6 in the presence of **3a** in *d*8-toluene resulted only in the formation of one main phosphorus species at lower field $\delta = 58.28$ ppm, which indicates no formation of the oxidative addition product under these conditions.

To demonstrate the generality of our catalyst systems for other carbonylations as well, reactions of vinyl triflates in the presence of other nucleophiles (alcohols, phenol, and amines)

were performed. As shown in Scheme 3, alcohols including methanol, *n*-butanol, and benzyl alcohol led to the

Scheme 3. Substrate Scope of Pd-Catalyzed Synthesis of α,β -Unsaturated Esters and Amides^a

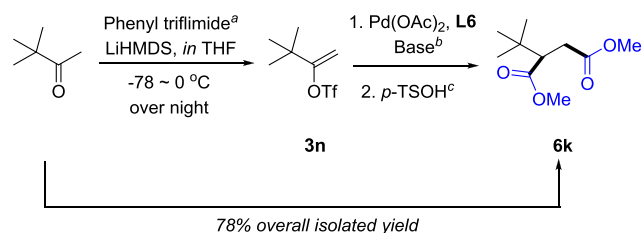


^aReaction conditions: 0.5 mmol of **3**, 2 equiv of nucleophiles (1.2 equiv for **5d**, **5e**, **5g**, **5i**, and **5j**), Ar. Yields of isolated products. ^bGC yield. ^cWith 1.5 equiv of TMEDA, *L*-proline methyl ester hydrochloride as nucleophile, two rotameric isomers of the product presented with a ratio of 3:1 according to ¹H NMR.

corresponding esters **5a–5d** with six- or seven-membered rings in up to 94% yield. Even less basic phenol reacted smoothly with cyclohexenyl triflate to give the corresponding product in 84% isolated yield (**5e**). With respect to amines, both primary and secondary amines, including anilines and aliphatic ones as well as *L*-proline methyl ester hydrochloride, were converted successfully to the desired products (**5f–5j**).

Due to the excellent performance of this catalyst in various carbonylation reactions, the here-reported procedure can be easily combined with a subsequent olefin carbonylation step. Hence, it is possible to access a variety of dicarbonylated products in only two steps from the corresponding ketone using the same catalyst system (Scheme 4). To demonstrate this principle **3n** was synthesized in the first step, and after simply adding 16 mol % PTSA·H₂O, the dicarbonylated

Scheme 4. General Strategy for the Synthesis of Dicarbonylated Products from the Corresponding Ketones



^aPhenyl triflimide = *N*-phenyl-bis(trifluoromethanesulfonimide). ^b0.5 mmol of **3n**, 1 mol % Pd(OAc)₂, 1.5 mol % L6, 0.55 equiv of TMEDA, 2 mL of MeOH, 5 bar CO, 60 °C, 16 h, Ar. ^cIn situ addition of 16 mol % PTSA·H₂O, 40 bar CO, 120 °C, 16 h, argon atmosphere.

compound **6k** was isolated in 78% overall yield (see the SI, Scheme S2).

In conclusion, we have developed an efficient and general protocol for the synthesis of α,β -unsaturated aldehydes, esters, and amides under mild conditions using the specific palladium/L6 catalyst system. For the first time, we demonstrate that the incorporation of basic pyridyl-substituents significantly improves the performance of the catalyst in palladium-catalyzed coupling processes. The synthetic utility of the protocol is demonstrated in the carbonylation of vinyl triflates including derivatives of camphor, ketoisophorone, verbenone, and pulegone. Furthermore, this catalyst system allows for an easy access of dicarbonylated products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00765.

Additional methods, procedures, data, and figures including structures, syntheses, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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