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Pd-catalyzed synthesis of α,β-unsaturated ketones by carbonylation of vinyl triflates and nonaflates†

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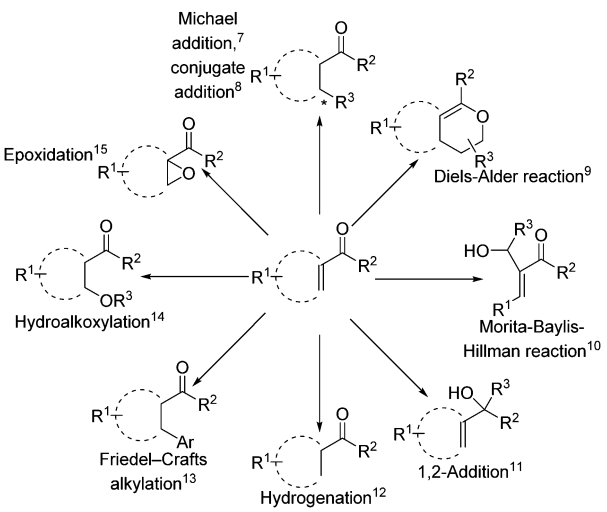
A general and highly chemoselective Pd-catalyzed protocol for the synthesis of α,β-unsaturated ketones by carbonylation of vinyl triflates and nonaflates is presented. Applying the specific monophosphine ligand cataCXium® A, the synthesis of various vinyl ketones as well as carbonylated natural product derivatives proceeds in good yields.

α,β-Unsaturated ketones represent a class of highly valuable intermediates in organic synthesis, which continue to attract the interest of academic and industrial researchers for various applications.[1] As illustrated in Scheme 1, a wide range of diverse compounds including pharmaceuticals,[2] polymers,[3] flavors,[4] and biologically[5] or optically[6] important molecules can be conveniently synthesized from such starting materials.

Traditionally, α,β-unsaturated ketones are synthesized *via* multistep reactions, *e.g.* sulfide or sulfoxide dehydrogenation,[16] enamine transformations,[17] Aldol[18] or Knoevenagel condensation,[19] as well as the so-called Saegusa oxidation.[20] More recently, protocols based on the dehydrogenation of ketones,[21] alcohols[22] and alkenes,[23] or the carbonylation of alkynes[24] and vinyl iodides,[25] *etc.*[26] became popular, too. Despite all these achievements, the search for alternative procedures for this class of building blocks remains a challenging but rewarding task.



Scheme 1 Selected transformation of α,β-unsaturated ketones.

Based on our long standing interest in reductive carbonylations and alkoxycarbonylations,[27] we envisioned the synthesis of α,β-unsaturated ketones *via* carbonylative coupling reactions of phenylboronic acids and CO with vinyl triflates or nonaflates easily derived from ketones. Herein, we report a general and selective palladium catalyst system which allows for such transformations.

In our initial experiments, we investigated the carbonylation of cyclohexenyl triflate (**1**) in the presence of phenylboronic acid using previously optimized carbonylative coupling reaction conditions (1 mol% $Pd(OAc)_2$, 1.5 mol% ligand, 0.75 eq. TMEDA in 2 mL toluene with 5 bar CO).[28] As shown in Scheme 2, standard mono- and bidentate phosphines, focusing especially on bulky ligands, were tested for this benchmark reaction. Ligands **L1** and **L2** with integrated basic sites (pyridine), which recently have been proven to be highly efficient in various carbonylation reactions,[29] as well as commercially available ligands **L3–L6** were not suitable for this transformation giving in general low or no yield of the desired product **3**. Here, in most cases decomposition of the substrate was observed. In contrast, when applying **cataCXium® A** ($BuPAd_2$, **L7**), the reaction proceeded extremely well to give the desired product in quantitative yield (99%). Based on this result of **cataCXium® A**, we also tested other sterically hindered adamantyl-substituted ligands (**L8–L11**), however, **3** was obtained in only 48% or lower yield.[30]

Next, critical reaction parameters including [Pd] and ligand concentration, temperature, and solvent were investigated. As shown in Table 1, control experiments without $Pd(OAc)_2$ and/or ligand revealed no formation of the desired product (Table 1, entries 2–4). Notably, the catalyst loading can be decreased to only 0.1 mol% resulting in a slight decrease of the yield from 99% to 82% (Table 1, entries 5–7), which indicated the efficiency

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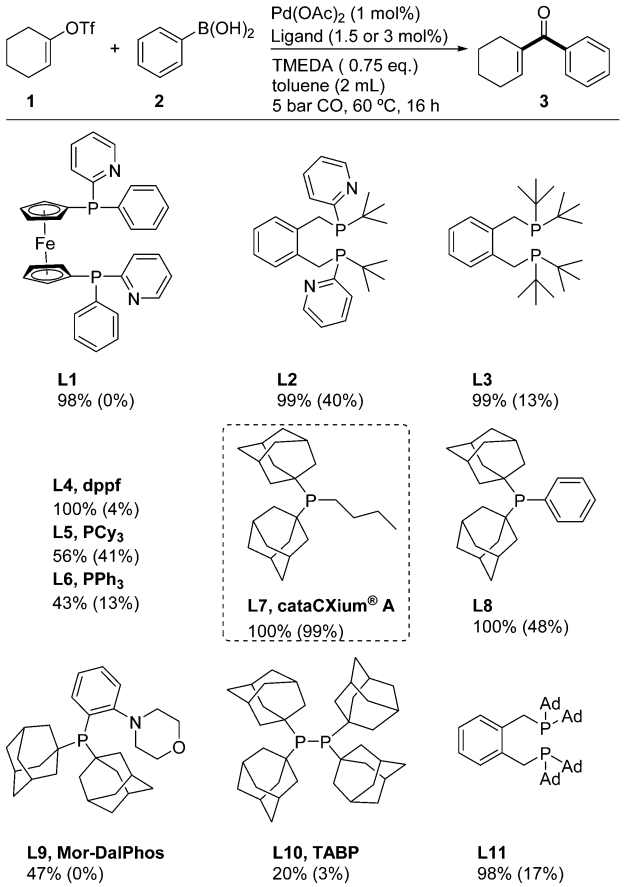
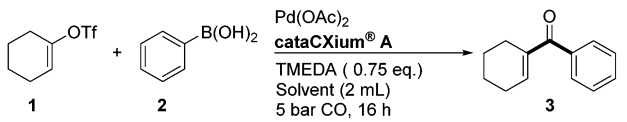


Scheme 2 Pd-catalyzed synthesis of 1-cyclohexenyl phenyl ketone in the presence of different ligands. Reaction conditions: 0.5 mmol **1**, 1.2 eq. of **2**, 1.5 mol% for diphosphines, 3 mol% for monophosphines, in argon. Yields and conversions were determined by GC with *n*-hexadecane as standard, the values given within parentheses refer to the yields of **3** while the other values refer to the conversions of **1**.

Table 1 Pd-catalyzed synthesis of 1-cyclohexenyl phenyl ketone under various conditions



Entry	$Pd(OAc)_2$/mol%	cataCXium® A/mol%	Solvent	T/°C	Conv. (yield)/%
1	1	3	Toluene	60	100 (99)
2	1	0	Toluene	60	20 (0)
3	0	3	Toluene	60	0 (0)
4	0	0	Toluene	60	11 (0)
5	0.5	1.5	Toluene	60	100 (99)
6	0.1	0.3	Toluene	60	98 (82)
7	0.05	0.15	Toluene	60	72 (40)
8	0.1	0.3	THF	60	96 (56)
9	0.5	1.5	Toluene	40	75 (46)
10	0.5	1.5	Toluene	25	29 (12)

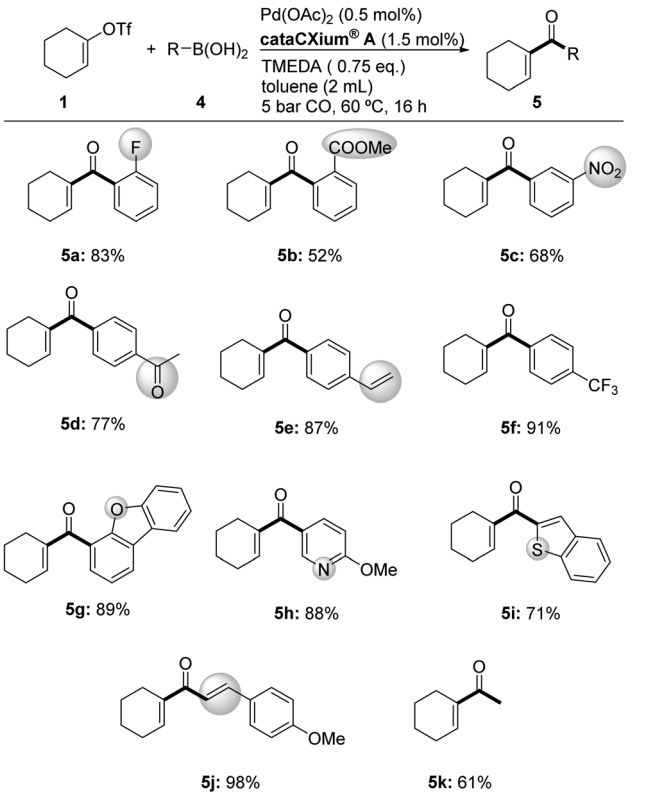
Reaction conditions: 0.5 mmol **1**, argon atmosphere. Yields and conversions were determined by GC with *n*-hexadecane as standard.

of this catalytic system. Best results for the benchmark reaction at low catalyst loading were obtained at 60 °C and experiments at R.T. or 40 °C showed a significant decrease of the yield of **3** to 12 and 46%, respectively (Table 1, entries 9 and 10).

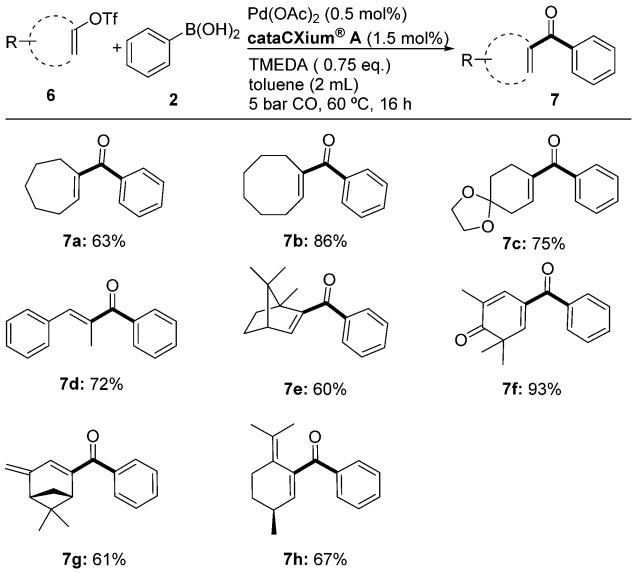
With the optimized reaction conditions in hand, carbonylations of **1** with CO and structurally diverse boronic acids were performed (Scheme 3). Besides phenylboronic acid, eleven other substrates were converted to the corresponding products **5a–5f** in moderate to excellent yields (52–91%). Here, various arylboronic acids substituted by –F, –COOMe, $–NO_2$, –COMe, $–CH{=}CH_2$, and $–CF_3$ in either *ortho*-, *meta*-, or *para*-position gave the desired ketones. In addition, heterocyclic substrates including furan, pyridine, and thiophene derivatives are converted smoothly to the corresponding vinyl heteroaryl ketones in 71–89% yields (**5g–5i**). Notably, vinyl boronic acid was tested too, yielding 98% of the desired divinyl ketone **5j**, which provides possibilities for interesting cyclization reactions.[31]

Apart from aromatic and vinyl boronic acids, also methyl boronic acid can be employed in this transformation to access methyl vinyl ketones, *e.g.* **5k**, which constitute key synthetic intermediates.[32]

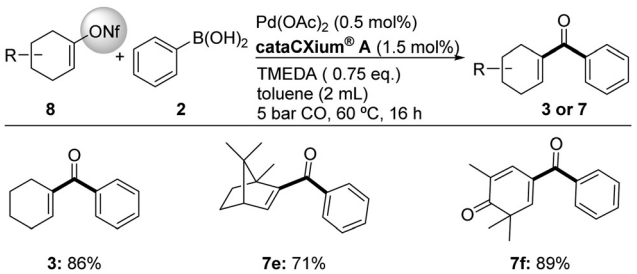
Next, we studied the carbonylation of structurally diverse triflates with CO and phenylboronic acid. As shown in Scheme 4, vinyl triflates with seven- and eight-membered rings were carbonylated successfully under optimized conditions to give **7a** and **7b**. Similarly, **7c** was isolated in 75%. Obviously, this procedure is not limited to cyclic substrates. As an example, the linear vinyl ketone **7d** was obtained in 72% yield. Furthermore, functionalization of naturally occurring terpenes can be easily achieved. Hence, derivatives of camphor, ketoisophorone, verbenone, and pulegone



Scheme 3 Pd-catalyzed synthesis of 1-cyclohexenyl aryl ketones. Reaction conditions: 0.5 mmol **1**, 1.2 eq. of **4**, in argon. Isolated yields.



Scheme 4 Pd-catalyzed synthesis of vinyl phenyl ketones. Reaction conditions: 0.5 mmol **6**, 1.2 eq. of **2**, in argon. Isolated yields.

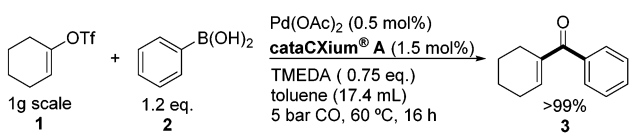


Scheme 5 Pd-catalyzed synthesis of vinyl phenyl ketones from vinyl nonaflates. Reaction conditions: 0.5 mmol **8**, 1.2 eq. of **2**, in argon. GC yields with *n*-hexadecane as internal standard.

are smoothly converted to the corresponding vinyl ketones under standard conditions in good isolated yields (**7e–7h**).

From a synthetic point of view, the use of more stable triflate analogues is interesting due to the easier handling and the avoidance of unwanted side reactions. In this respect, the use of vinyl nonafluorobutanesulfonates (vinyl nonaflates) for the carbonylative synthesis of α,β-unsaturated ketones is appealing. As exemplified in Scheme 5, several nonaflates underwent smooth transformations in up to 89% yield of the desired products **3**, **7e** and **7f**.

Furthermore, our catalytic system was tested on 1 g scale. As showed in Scheme 6, cyclohexenyl triflate **1** was successfully converted to the corresponding carbonylated product **3** in >99% yield.



Scheme 6 Gram scale synthesis of 1-cyclohexenyl phenyl ketone. Yield was determined by GC with *n*-hexadecane as standard.

In conclusion, we present a convenient and general procedure for the synthesis of α,β-unsaturated ketones under mild conditions. Using the palladium acetate in combination with the monophosphine ligand **cataCXium® A** a variety of such products including aliphatic, (hetero)aromatic and divinyl ketones can be efficiently accessed. For the first time, in this procedure we adapted vinyl triflates for the synthesis of α,β-unsaturated ketones with CO as carbonylation partner. 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 is applicable for the carbonylation of more stable nonaflates.

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Conflicts of interest

There are no conflicts to declare.

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