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A Direct Amine-Palladium Acetate Cocatalyzed Saegusa Oxidation Reaction of Unmodified Aldehydes to α,β-Unsaturated Aldehydes

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Abstract: A direct preparation of synthetically useful α,β-unsaturated aldehydes from readily available aldehydes has been developed. The process is effectively cocatalyzed by an amine-palladium acetate to give rise to α,β-unsaturated aldehydes in moderate to good yields (41–62%). The reaction features the use of unmodified aldehydes rather than enol silyl ethers, which are used in a typical Saegusa oxidation reaction.

Keywords: aminocatalysis; organocatalysis; Saegusa reaction; α,β-unsaturated aldehydes

α,β-Unsaturated aldehydes are highly useful synthetic building blocks in organic synthesis.[1] Recently their synthetic utility has been significantly expanded by organocatalysis. Notably they are the most commonly used substrates in organocatalyzed asymmetric reactions[2–4] and powerful cascade processes.[5,6] They serve as effective electrophiles for a variety of organic transformations, in particular conjugate addition processes.

Despite their broad synthetic utility, the synthesis of α,β-unsaturated aldehydes is still a tedious and challenging task. Several approaches to effect this operation have been disclosed over the years.[7] The general strategies rely on functional group interconversion involving multi-step transformations. Among these processes are the oxidation of allylic alcohols,[8] the Peterson olefination,[9] or the formylation.[10,11] The cross-metathesis reactions of acrolein[12] and cross-aldol condensations[13] are alternative tactics. The latter suffers from several side reactions under relatively strong basic conditions, self-aldolization, and narrow substrate diversity. Furthermore, they can be accessed in high efficiency by way of the Wittig olefination using formylmethylenetriphenylphosphorane with only electron-poor aldehydes.[14] The oxidation-elimination of highly toxic selenium aldehydes in one- or two-step protocols is another important approach to α,β-unsaturated carbonyls.[15] It is noteworthy that most of the described methods produce equimolar amounts of by-products and thus render them not atom-economic. Accordingly, the development of catalytic reactions using readily available chemicals is of considerable significance in the synthesis of versatile α,β-unsaturated aldehydes.

The Saegusa oxidation is a convenient method for the conversion of a silyl enol ether into the corresponding α,β-unsaturated aldehydes and ketones [Figure 1, Eq. (1)].[16,17] The attractive features of the Saegusa oxidation include the use of a catalytic amount of $Pd(OAc)_2$ as catalyst and O_2 as oxidant. However, the approach requires the preformation of silyl enol ethers from the corresponding aldehydes and ketones.[17]

The direct oxidation of aldehydes or ketones with O_2 in the presence of a catalytic amount of $Pd(OAc)_2$ is a particularly attractive strategy for the synthesis of α,β-unsaturated carbonyl compounds since the substrates are readily available or easily prepared and O_2

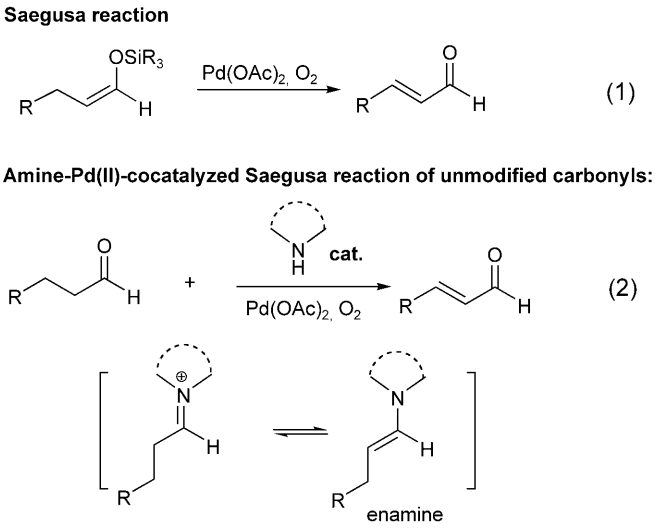
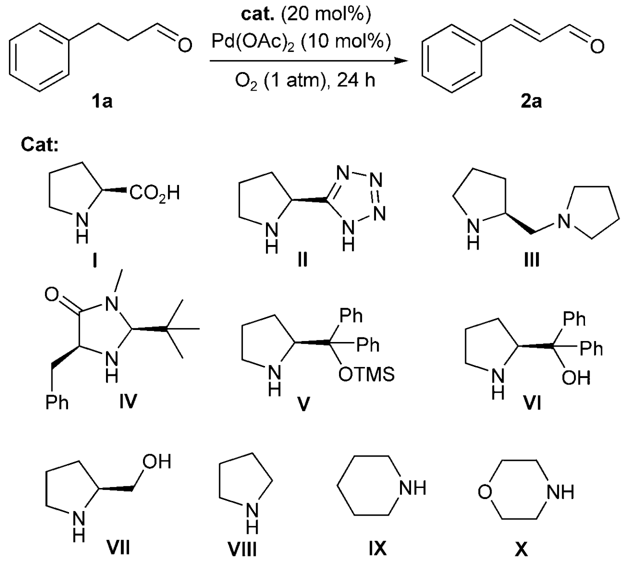


Figure 1. The Pd(II)-catalyzed Saegusa reaction.

Table 1. Results of exploratory studies on the amine-$Pd(OAc)_2$ cocatalyzed Saegusa reaction of 3-phenylpropionaldehyde (**1a**) to cinnamaldehyde (**2a**).[a]



Entry	Cat.	Solvent	T [°C]	Yield[b] [%]
1	**I**	DMSO	30	no reaction
2	**II**	DMSO	30	no reaction
3	**III**	DMSO	30	no reaction
4	**IV**	DMSO	30	4
5	**V**	DMSO	30	48
6	**V**	DMSO	60	30
7	**VI**	DMSO	30	38
8	**VI**	**DMSO**	**60**	**62**
9	**VI**	DMSO	100	32
10	**VI**	DME	60	14
11	**VI**	THF	60	12
12	**VI**	CH_3CN	60	17
13	**VI**	toluene	60	5
14	**VII**	DMSO	30	24
15	**VIII**	DMSO	30	57
16	**VIII**	DMSO	60	24
17[c]	**VIII**	DMSO	30	no reaction
18	**IX**	DMSO	30	35
19	**X**	DMSO	30	35

[a] *Reaction conditions:* see Experimental Section.

[b] Isolated yields.

[c] 100 mol% **V**.

is used as oxidant. Nevertheless, studies have shown that very low reaction yields are obtained for the direct dehydrogenation of aldehydes and ketones.[18] Given the great success of amine-promoted iminium/enamine reactions of aldehydes and ketones, we envisioned that the combination of the aminocatalysis with the $Pd(OAc)_2$-mediated Saegusa oxidation could result in a new direct approach to α,β-unsaturated carbonyl compounds from aldehydes and ketones (Figure 1). In the proposed process, the reaction of an aldehyde or a ketone with an amine catalyst generates an enamine, which is considered as an equivalent of the silyl enol ether in a typical Saegusa oxidation reaction. The *in situ* formed enamine can be subsequently oxidized to an enal or enone by O_2 in the presence of $Pd(OAc)_2$.

To demonstrate the possibility of the amine-$Pd(OAc)_2$ cocatalyzed direct oxidation of aldehydes to α,β-unsaturated carbonyl compounds, we have conducted a model reaction of 3-phenylpropionaldehyde **1a** in the presence of an amine (20 mol%), $Pd(OAc)_2$ (10 mol%) and O_2 (1 atm) in DMSO at 30 °C for 24 h (Table 1). The preliminary investigations revealed that the reaction occurred as designed. Nevertheless, the reaction efficiency was highly amine catalyst dependent. No reactions occurred when proline **I**, (*S*)-pyrrolidine-tetrazole **II** and diamine **III** were employed (entries 1–3). MacMillan's catalyst **IV** also displayed very poor catalytic activity towards the process (entry 4). Among the catalysts probed, diphenylprolinol TMS ether **V**, diphenylprolinol **VI**, prolinol **VII** and simple pyrrolidine **VIII**, piperdine **IX** and morpholine **X** provided encouraging outcomes (entries 5, 7, 14, 15, 18 and 19) and moderate to good yields (38–62%) were achieved. Interestingly, on elevating the reaction temperatures from 30 °C to 60 °C with catalysts **V**, **VI** and **VIII**, mixed results were observed (entries 6, 8 and 16). Lower reaction yields (30 and 24%, entries 6 and 16) were obtained with catalysts **V** and **VIII**, while diphenylprolinol **VI** afforded a higher yield (62%, entry 8). Further raising the temperature to 100 °C did not give any improvement (entry 9). Probing the solvent effect on the process indicated that the reaction medium had an important impact (entries 8, and 10–13). The best result was obtained when the reaction was carried out in DMSO (entry 8). It is noted that under the reaction condi-

Table 2. Scope of the amine-$Pd(OAc)_2$ cocatalyzed direct Saegusa reactions.[a]

Entry	R, R′	t [h]	T [°C]	Yield[b] [%]
1	C_6H_5, H, **2a**	24	60	62
2	4-MeO-C_6H_4, H, **2b**	24	45	58
3	2-MeO-C_6H_4, H, **2c**	24	45	41
4	2-Me-C_6H_4, H, **2d**	20	60	60
5	4-CN-C_6H_4, H, **2e**	23	45	53
6	4-NO_2-C_6H_4, H, **2f**	8	45	43
7	4-Cl-C_6H_4, H, **2g**	24	60	45
8	2,4-$Cl_2C_6H_3$, H, **2h**	24	60	53
9	4-MeCO-C_6H_4, H, **2i**	8	60	57
10	4-MeOCO-C_6H_4, H, **2j**	9	45	49
11	$C_6H_5CH_2$, H, **2k**	24	60	no reaction
12	C_6H_5, Me, **2l**	24	60	no reaction
13	C_6H_5, OMe, **2a**	24	60	no reaction

[a] *Reaction conditions:* see Experimental Section.

[b] Isolated yields.

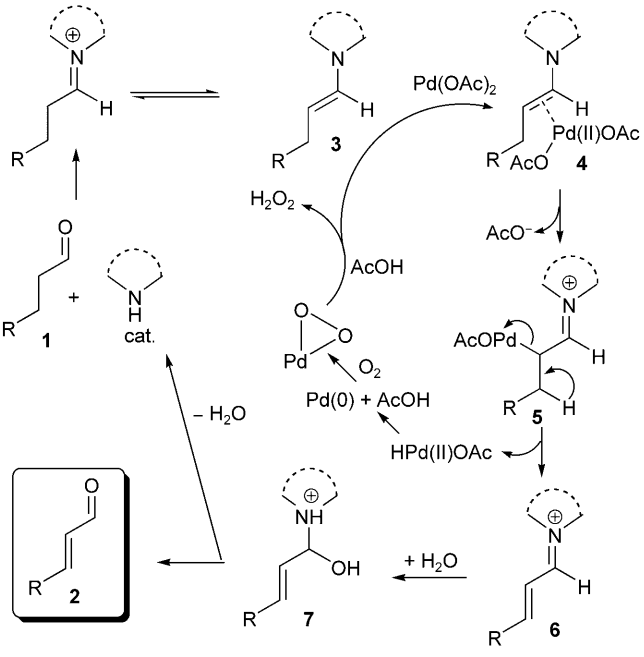


Figure 2. A plausible mechanism for the amine-$Pd(OAc)_2$ cocatalyzed conversion of 3-substitued propionaldehydes to 3-substitued acroleins.

tions, the aldehyde was not oxidized to the corresponding carboxylic acid.

The conditions that proved optimal for the dehydration of 3-phenylpropionaldehyde (**1a**) to cinnamaldehyde (**2a**), cocatalyzed by **VI** (20 mol%) and $Pd(OAc)_2$ (10 mol%) in DMSO in the presence of O_2 (1 atm) were applicable for the Saegusa oxidation of other aldehydes (Table 2). The aromatic rings of the aldehydes bearing electron-neutral (entry 1), electron-donating (entries 2–4) or electron-withdrawing (entries 5–10) substituents underwent the reaction smoothly affording the desired products in moderate to good yields (41–62%). These outcomes implied that the electronic features had only a marginal effect on the processes. Examination of the results of the investigation also revealed that the steric effect (*o*- *vs.* *p*-substitution pattern) also played a minimal role in governing the reaction's efficiency. A limitation is also realized for the amine-$Pd(OAc)_2$ cocatalyzed Saegusa oxidation reaction. No reaction occurred with aliphatic aldehydes, ketones and esters (entries 11–13).

A possible pathway of the amine-$Pd(OAc)_2$ cocatalyzed Saegusa oxidation reaction is proposed based on the established typical Saegusa oxidation reaction mechanism (Figure 2).[19] In analogy to a typical Saegusa oxidation reaction of silyl enol ethers,[19] an enamine **3** is initially formed from the corresponding aldehyde. Coordination of the enamine **3** with $Pd(OAc)_2$ leads to an alkene-Pd complex **4**, which subsequently transforms to a palladium adduct **5**, an intermediate similar to that in the classic Saegusa oxidation.[19] β-Hydride elimination of HPdOAc gives rise to the iminium **6**. Upon hydrolysis, this will furnish the enone and regenerate the aminocatalyst. Meanwhile, reductive elimination of HPdOAc affords Pd(0), which is subsequently oxidized by O_2 to Pd(II) for the next cycle reaction. It is reasonably surmised that 3-arylpropionaldehydes through a conjugation effect can more effectively facilitate the elimination reaction, and accordingly only they can efficiently participate in the process.

In summary, this investigation has resulted in a new direct Saegusa oxidation reaction of unmodified aldehydes. This process, catalyzed by a combination of organocatalyst (an amine) and an organometallic $[Pd(OAc)_2]$, affords synthetically useful α,β-unsaturated aldehydes in moderate to good yields. Therefore, the studies have significantly expanded the scope of organocatalysis and afford a new alternative approach to the preparation of enals. Further investigations on this valuable transformation with a focus on expanding the scope (ketones as substrates) and other applications are underway in our laboratory.

Experimental Section

Typical Procedure (Table 2, entry 1)

A mixture of 3-phenylpropanal (60 mg, 0.45 mmol), (*S*)-diphenylprolinol (**VI**) (23 mg, 0.09 mmol), $Pd(OAc)_2$ (10 mg, 0.045 mmol), and DMSO (1 mL) was stirred for 24 h at 60 °C in an atmosphere of oxygen. The crude product was purified by column chromatography on silica gel (30/1 v/v *n*-hexane/ethyl acetate) to give the desired product cinnamaldehyde; yield: 62%. ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 6.73$ (dd, 1H, $J = 7.6$ and 16.0 Hz), 7.43–7.45 (m, 4H), 7.49 (d, 1H, $J = 16.0$ Hz), 7.56–7.59 (m, 2H), 9.71 (d, 1H, $J = 7.6$ Hz); ^{13}C NMR ($CDCl_3$, 400 MHz): $\delta = 128.5$, 128.6, 129.1, 131.2, 134.0, 152.7, 193.7; MS (EI): $m/z = 132$ (M^+), 131 (100%).

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