Palladium-catalyzed Decarboxylative [4 + 1] Cyclization of γ-Methylidene-δ-valerolactones with Isocyanides

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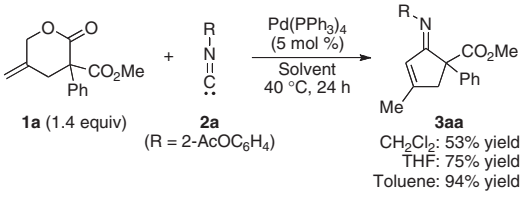
A palladium-catalyzed decarboxylative cyclization of γ-methylidene-δ-valerolactones with isocyanides has been developed to afford conjugated cyclopentenimines under mild conditions. Some preliminary results toward the development of an asymmetric variant have also been described.

Carbon monoxide has been widely utilized as a source of one-carbon unit in various transition-metal-catalyzed cycloaddition reactions (e.g., the Pauson–Khand reaction[1]) to produce cyclic ketones with high efficiency.[2] In contrast, isoelectronic isocyanides are often used in cycloaddition reactions as a source of N–C or C–N–C fragment in a cyclic framework for the synthesis of nitrogen-containing heterocycles.[3,4] In fact, only a few reports have been made on the use of isocyanides as a surrogate of carbon monoxide to form cyclic ketimines under transition-metal catalysis,[5–7] and none of them have been applied to asymmetric variants so far. In this context, here we describe the development of a palladium-catalyzed decarboxylative cyclization of γ-methylidene-δ-valerolactones[8] with isocyanides to obtain cyclopentenimines under mild conditions, including our preliminary results in its application to asymmetric catalysis.[9]

We initiated our study by conducting a reaction of γ-methylidene-δ-valerolactone **1a** with 2-acetoxyphenyl isocyanide[10] (**2a**) in the presence of 5 mol % $Pd(PPh_3)_4$ as a catalyst in CH_2Cl_2 at 40 °C (eq 1). The decarboxylative [4 + 1] cyclization product was successfully obtained as conjugated cyclopentenimine **3aa** in moderate yield (53% yield). We subsequently found that higher yield of **3aa** can be achieved by conducting the reaction in THF (75% yield) or in toluene (94% yield). Under the conditions using toluene as the solvent, several other α-(hetero)aryl-γ-methylidene-δ-valerolactones **1** can also be used for the synthesis of cyclopentenimines **3** with isocyanide **2a** in high yield (83–97% yield; Table 1, Entries 1–5).[11] With respect to the nitrogen-substituent on isocyanide, various bulky aryl groups are well suited under the present conditions (75–94% yield; Entries 6–9), and a different set of conditions is necessary to effectively employ an aryl group with no substituents at the ortho-positions (dppf as the ligand; Entry 10). In addition to aryl isocyanides, alkyl groups are also tolerated, giving cyclization products **3** in good yield (62% yield; Entry 11).[12]

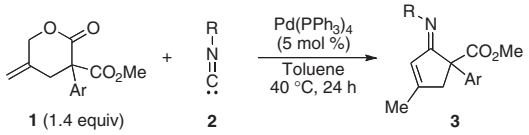


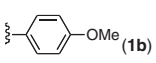
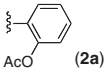
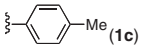
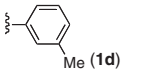
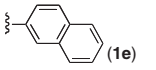
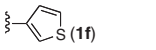
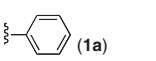
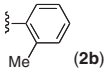
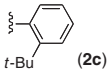
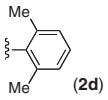
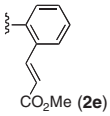
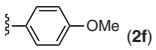
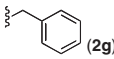
(1)

A proposed catalytic cycle of this process is illustrated in Figure 1. Thus, oxidative addition of the allyl ester moiety of **1** to palladium(0), followed by decarboxylation,[13,14] gives 1,4-zwitterionic species **A**. The anionic carbon of **A** then attacks the carbon atom of **2** to give intermediate **B**, which undergoes a ring-closure through a nucleophilic attack of the same carbon atom to the π-allylpalladium moiety, leading to the formation of five-membered carbocycle **C** along with regeneration of palladium(0). Initially formed **C** having an exo-methylene readily isomerizes to more stable conjugated cyclopentenimine **3**.[15]

It is worth noting that the use of lactone **1g** having a methyl group at the δ-position in the reaction with **2a** selectively gives

Table 1. Palladium-catalyzed decarboxylative cyclization of γ-methylidene-δ-valerolactones **1** with isocyanides **2**



Entry	Ar	R	Product	Yield/%[a]
1	 (**1b**)	 (**2a**)	**3ba**	87
2	 (**1c**)		**3ca**	83
3	 (**1d**)		**3da**	97
4[b]	 (**1e**)		**3ea**	85
5	 (**1f**)		**3fa**	93
6	 (**1a**)	 (**2b**)	**3ab**	75
7		 (**2c**)	**3ac**	79
8		 (**2d**)	**3ad**	94
9		 (**2e**)	**3ae**	81
10[c]		 (**2f**)	**3af**	72
11		 (**2g**)	**3ag**	62[d]

[a]Isolated yield after chromatography on silica gel. [b]2.0 equiv of **1e** was used. [c]$PdCp(\eta^3\text{-}C_3H_5)$/dppf (5 mol %) was used as the catalyst. [d]Determined by ^1H NMR against internal standard (*p*-xylene) after chromatography on alumina.

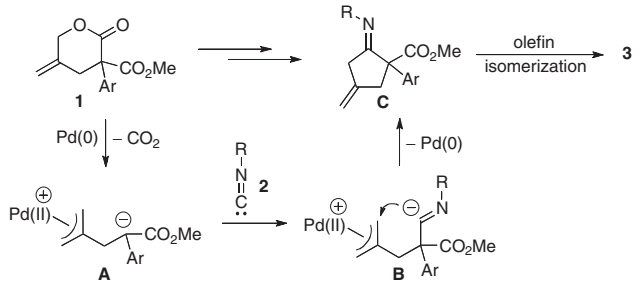
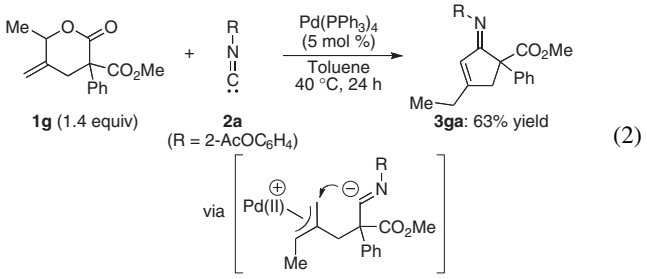


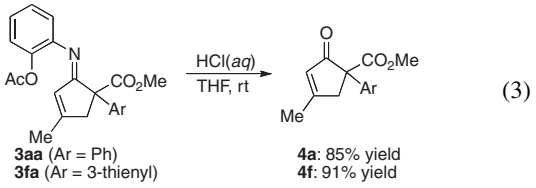
Figure 1. Proposed catalytic cycle for the palladium-catalyzed decarboxylative [4 + 1] cyclization of **1** with **2**.

ethylcyclopentenimine **3ga** through a ring closure at the less substituted carbon atom of a π-allylpalladium intermediate as shown in eq 2.



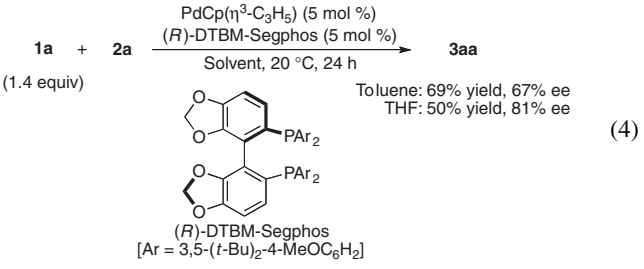
(2)

Of course, the imines that are obtained under the present catalysis can be easily hydrolyzed to give the corresponding cyclopentenones in high yield by treating them with aqueous HCl in THF (85–91% yield; eq 3).



(3)

We have also begun to explore the development of an asymmetric variant of this process. Thus, through a brief survey of chiral ligands[16] in the reaction of **1a** with **2a** in toluene, we found that the use of (*R*)-DTBM-Segphos[17] gave product **3aa** with promising ee of 67% (eq 4). By changing the solvent to THF, the enantioselectivity could be further improved to 81% ee.



(4)

In summary, we have developed a palladium-catalyzed decarboxylative cyclization of γ-methylidene-δ-valerolactones with isocyanides to generate cyclopentenimines under mild conditions. The products thus obtained can be readily converted to the corresponding cyclopentenones upon selective hydrolysis of the imine. We have also described our preliminary results toward the development of an asymmetric variant. Future studies will focus on further improvement of the reaction conditions to achieve more efficient asymmetric catalysis.

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