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Metal–Ligand Cooperation in the Cycloisomerization of Alkynoic Acids with Indenediide Palladium Pincer Complexes

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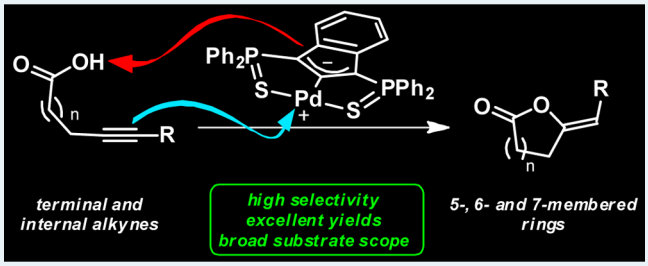
Supporting Information

ABSTRACT: Indenediide Pd complexes **1a–c** are shown to very efficiently catalyze the cycloisomerization of alkynoic acids into alkylidene lactones via metal–ligand cooperation (TON up to 2000). Complexes **1a–c** are competent toward a broad range of alkynoic acids, including functionalized and internal ones, and give access to 5- as well as 6- and 7-membered lactones in excellent yields and with very high selectivities.



KEYWORDS: *pincer complexes, metal–ligand cooperation, palladium, cycloisomerization, noninnocent ligand, homogeneous catalysis*

The efficiency of cooperative catalysis in biological systems has inspired chemists to design and develop molecular complexes in which metal and ligands act in concert to promote chemical processes. Here, the ligands not only modulate the stereoelectronic properties of the metals but also participate directly in the catalytic process (they are temporarily transformed and, thus, exhibit so-called noninnocent character). Such metal–ligand cooperation enables activation/formation of chemical bonds under mild conditions and represents a valuable alternative to the typical oxidative addition/reductive elimination pathways.[1]

This approach was initially developed by Noyori and Shvo with complexes of types **A**[2] and **B**,[3] whose ligands undergo reversible amine–amide and alcohol–ketone interconversions. Over the last two decades, spectacular progress has also been achieved in metal–ligand cooperative catalysis using pincer complexes (representative examples are given in Chart 1).[4−7] In particular, Milstein discovered an original aromatization/dearomatization process in pyridine- and acridine-based pincer complexes (complexes of type **C**)[4] This proved extremely efficient for the activation of a broad range of H–X bonds (X = H, aryl, OR, NR_2, ...) and led to spectacular catalytic developments.[4]

Although the concept of metal–ligand cooperative catalysis is relatively well-established, its development is still in his infancy, and much remains to be discovered in the field. In particular, the variety of ligand frameworks able to display noninnocent character is quite limited, and so far, the scope of concerned transformations, essentially hydrogenation/dehydrogenation processes, remains relatively narrow.

Recently, we described original pincer complexes of type **G** (Chart 2) in which two $Ph_2P{=}S$ side-arms support in-plane σ-coordination of the central indenyl moiety (instead of the most common facial π coordination).[8] According to analytical data and DFT calculations, complexes **G** are best described as indenediide Pd(II) complexes. The combination of an electrophilic Pd center and an electron-rich ligand backbone was substantiated experimentally by stoichiometric reactions at either the Pd center or the ligand backbone.[9] The noninnocent

Chart 1. Selected Examples of Metal-Ligand Cooperative Complexes

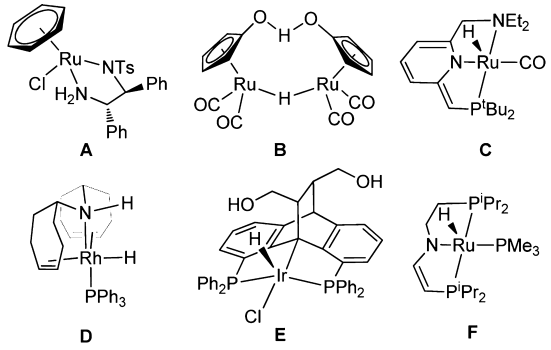
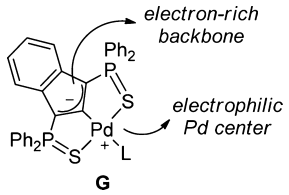


Chart 2. Indenediide Pd Pincer Complexes G



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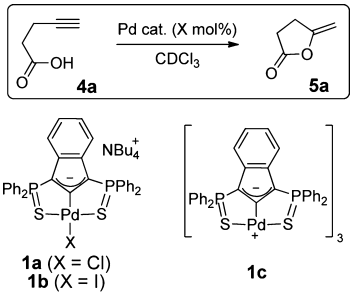
character of the indenediide ligand was also illustrated by the preparation of original polymetallic species.[10]

Here, we report on the catalytic applications of such indenediide Pd complexes involving metal−ligand cooperation. Complexes of type **G** are shown to efficiently promote the cycloisomerization of alkynoic acids (intramolecular addition of carboxylic acids to alkynes), offering a valuable alternative to the complexes commonly used to catalyze this transformation (Pd, Rh, Ru, Pt, Au).[11,12] With indenediide Pd complexes, no external base is needed, the alkylidene lactones are obtained with very high selectivities, and the reaction is unprecedentedly broad in scope.

The catalytic activity of indenediide Pd complexes was first evaluated in the cyclization of 4-pentynoic acid (**4a**) as the model reaction. The catalytic tests were carried out in $CDCl_3$ at room temperature, with 5 mol % of catalyst and in the absence of any base (Table 1). The reaction proceeds readily and

Table 1. Evaluation of the Catalytic Properties of the Indenediide Pd Complexes 1a−c in the Cyclization of 4-Pentynoic Acid 4a



entry[a]	cat.	Pd mol %	T (°C)	time (h)	conv (%)[b]
1	**1a**	5	25	1	99
2	**1b**	5	25	1	99
3	**1c**	5	25	1	99
4	**1b**	1	25	24	99
5[c]	**1b**	0.05	90	6	99

[a]All catalytic tests were performed under argon atmosphere starting from 0.2 mmol of 4-pentynoic acid (0.1 M in $CDCl_3$). [b]Conversions were determined by ^{1}H NMR and GC/MS analyses. [c]Reaction carried out on a 2 M solution of 4-pentynoic acid in $CDCl_3$.

exclusively via 5-exo-dig cyclization. Using the chloropalladate complex **1a** as the catalyst, 5-methylene-dihydrofuran-2-one (**5a**) is thereby obtained quantitatively after 1 h (entry 1).[13] Practically identical results were obtained with the neutral trimeric complex **1c** (entry 3),[14] indicating that the ionic character of **1a** and n-Bu_4N^+ countercation are not crucial. Replacing chloride for iodide at palladium did not induce a significant variation of catalytic activity either. With the iodopalladate **1b**,[14] the alkylidene lactone **5a** is also obtained quantitatively within ∼1 h under the same conditions (entry 2). The study was continued with complex **1b** because it is less soluble in low-polar solvents, which facilitates work-up and isolation of the formed lactones.[13] Recycling tests were then performed to assess the robustness of the system, and satisfyingly, no sign of catalyst deactivation was detected up to at least 10 cycles (after each cycle, the solvent was removed under vacuum and the lactone **5a** was extracted with diethyl ether).[13] To further evaluate catalytic performance, the catalyst loading was decreased. Using 1 mol %, longer reaction times were required at 25 °C (24 h), but the cyclization reaction again afforded quantitatively the alkylidene lactone **5a** (entry 4). Moreover, complete conversion could be attained within 6 h using only 0.05 mol % of complex **1b** (turnover number TON = 2000), carrying out the reaction at 90 °C and 2 M concentration (entry 5).

The scope of the reaction was then examined (Table 2). Several aims were pursued: (i) assess the generality of our cooperative catalyst and (ii) improve the catalytic transformation in terms of efficiency, selectivity, and scope. First, different substituents were introduced in the α position to the carboxylic acid. With ^{n}hex and CO_2Et groups, the cyclization proceeds readily and is actually faster than with the model substrate **4a** (most likely as the result of the Thorpe−Ingold effect) (entries 2 and 3). The related N-protected amino acid **4d** is only sparingly soluble in the reaction solvent and requires harsher conditions to be cyclized (90 °C over 12 h), but again, the corresponding γ-alkylidene lactone **5d** was obtained in quantitative yield (entry 4).[15] The exclusive formation of **5e** upon cyclization of the propargyl-allyl substrate **4e** (entry 5) illustrates the complete selectivity of the reaction in favor of alkynes over alkenes. We then varied the linker between the two reactive moieties. The rigidified substrate **4f** was quantitatively converted into the 3-methylene-3*H*-isobenzofuran-1-one **5f** in only 5 min at room temperature (entry 6). The length of the linker was then modulated, taking into account that the formation of 6- and 7-membered lactones is significantly more difficult to achieve than that of 5-membered lactones. Complex **1b** was able to promote the 6-exo cyclization of 5-hexynoic acid **4g** at 90 °C, and the corresponding 6-membered lactone **5g** was obtained in quantitative yield within 12 h (entry 7). This is among the best results obtained so far for this transformation.[12a,b,16]

We then turned to internal alkynoic acids that are much more challenging substrates than the terminal ones. At 90 °C, 3-pentynoic acid **4h** readily undergoes 5-endo-dig cyclization. The reaction is complete within 3 h, and lactone **5h** is obtained quantitatively (entry 8). With the homologous substrate **4i**, heating for 24 h at 90 °C was necessary to achieve complete conversion. Competition between 5-exo and 6-endo cyclizations leads in this case to a 3:1 mixture of the 5- and 6-membered lactones $\mathbf{5i}_{exo}$ and $\mathbf{5i}_{endo}$, respectively (entry 9). Importantly, $\mathbf{5i}_{exo}$ is obtained exclusively in its Z form (as established by comparing its NMR data with those reported in the literature).[17] This is consistent with activation of the C≡C triple bond by π-coordination to Pd and trans addition of the carboxylate moiety (see below for mechanistic discussion).[17] Complex **1b** also showed good activity in the cyclization of the rigid internal alkynoic acids **4j** and **4k** The reaction requires only 15−20 min at room temperature. In both cases, it is completely selective and affords a unique benzannelated lactone, but with a strong influence of the alkyne substituent: only 5-exo cyclization with Ph versus 6-endo cyclization with Cy (entries 10 and 11).[18] Last, the formation of 7-membered lactones was targeted,[19] and gratifyingly, the two δ-alkynoic benzoic acids **4l** and **4m** were found to be conveniently cyclized within 7−36 h at 90 °C (entries 12 and 13).

The fact that complexes **1a−c** promote the cyclization of **4a−m** without any additive is remarkable and contrasts with the known Pd-based catalysts that require the presence of 1.5−10 equiv of a base, typically a tertiary amine.[12] This has certainly to do with the properties of the employed ligand. As mentioned above, the indenediide backbone is electron-rich. It can thus behave as an internal base and catch temporarily the

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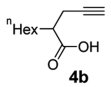
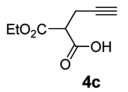
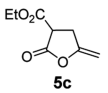
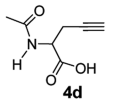
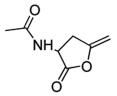
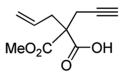
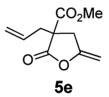
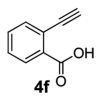
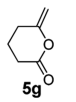
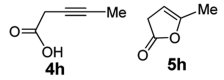
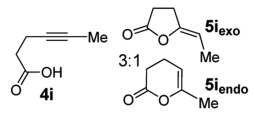
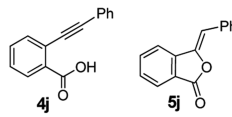
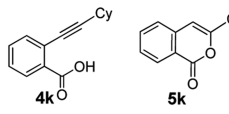
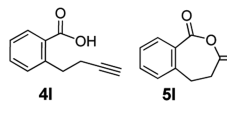
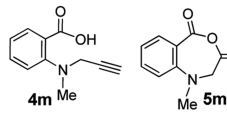
Table 2. Scope of the Pd-Catalyzed Cyclization of Alkynoic Acids (4a−m)

Entry[a]	Alkynoic Acid	Lactone	T (°C)	t (h)	Yield (%)[b]
1	 **4a**	 **5a**	25	1 h	99[c]
2	 **4b**	 **5b**	25	25 min	99 (99)
3	 **4c**	 **5c**	25	15 min	99 (97)
4	 **4d**	 **5d**	90	12 h	99 (97)
5	 **4e**	 **5e**	25	90 min	99 (85)
6	 **4f**	 **5f**	25	5 min	99
7	 **4g**	 **5g**	90	12 h	99 (97)
8	 **4h**	**5h**	90	3 h	99[c]
9	 **4i**	**5i**$_{exo}$ / **5i**$_{endo}$ (3:1)	90	24 h	95[c]
10	 **4j**	**5j**	25	15 min	99 (88)
11	 **4k**	**5k**	25	20 min	99 (98)
12	 **4l**	**5l**	90	36 h	95 (65)
13	 **4m**	**5m**	90	7 h	99 (91)

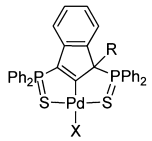
[a]Catalytic reactions performed under argon atmosphere using 0.2 mmol of the corresponding alkynoic acid **4a−m** (0.1 M in $CDCl_3$) and 5 mol % of the iodopalladate **1b**. [b]Conversions were determined by ^1H NMR and GC/MS analyses. Isolated yields are given in brackets. [c]The high volatility of the compound prevented accurate determination of the isolated yield.

acidic proton of the substrate. To corroborate this scheme, derivatives **1a−c** have been compared with the related 2-indenyl complexes **2a** and **3a,b**,[14,20] in which the ligand backbone is protonated or methylated at C1 (Table 3). No reaction at all was observed with **2a** and **3a** (entries 1 and 2), and cyclization of **4a** proceeds very slowly with **3b** (15% conversion after 24 h at room temperature, entry 3).

To further corroborate the cooperation between the electron-rich indenediide backbone and the metal, the catalytic activity of the iodopalladate **1b** was compared with that of the corresponding 2-indenyl complex **3b** combined with Et_3N as an external base. Cyclization of 4-pentynoic acid **4a** proceeds with the bicomponent system, but it is noticeably slower than with **1b** alone: only 51% conversion after 2h with **3b** + Et_3N (entry 4), although the reaction is complete within 1 h with **1b**. The iodopalladate **1b** also displays significantly higher activity than the bicomponent system **3b** + Et_3N in the cyclization of **4m**, a more challenging substrate (see Supporting Information Figure S3),[13] corroborating metal−ligand cooperation.

All these observations strongly argue in favor of an active participation of the indenediide motif in the catalytic transformation, and the following simplified catalytic cycle can be proposed for the cyclization of alkynoic acids catalyzed by the palladates **1a,b** (Scheme 1): (i) activation of the substrate by protonation of the ligand backbone at C1 and coordination of either the carboxylate or the alkyne to palladium (complexes of type **I** and **II**, respectively);[21] (ii) cyclization to give an alkenyl complex of type **III**; and finally, (iii) liberation of the alkylidene lactone by back-transfer of the proton from the ligand backbone and regeneration of the palladate.[22] At this point, cyclization reactions were carried out starting from 4-pentynoic acid labeled with deuterium either at the carboxylic acid (COOD) or at the alkyne (C≡CD) moiety. In both cases, the deuterium labeling was retained, and no scrambling was detected.[13] The obtained alkylidene lactone **5a** was selectively deuterated trans to O in the case of the CO_2D substrate (cis to O in the case of the C≡CD substrate), consistent with the proposed scenario.

Table 3. Indenyl Pd Complexes 2a and 3a,b Evaluated in the Cyclization of 4-Pentynoic Acid 4a



2a (R = H, X = Cl)
3a (R = Me, X = Cl)
3b (R = Me, X = I)

entry[a]	cat.	Pd mol %	*T* (°C)	time (h)	conv. (%)[b]
1	**2a**	5	25	36	0
2	**3a**	5	25	24	0[c]
3	**3b**	5	25	24	15
4	**3b** + Et_3N	5[c]	25	2	51

[a]Catalytic tests were performed under argon atmosphere starting from 0.2 mmol of 4-pentynoic acid (0.1 M in $CDCl_3$). [b]Conversions were determined by ^1H NMR analyses. [c]Reaction carried out with 5 mol % Pd and 5 mol % Et_3N.

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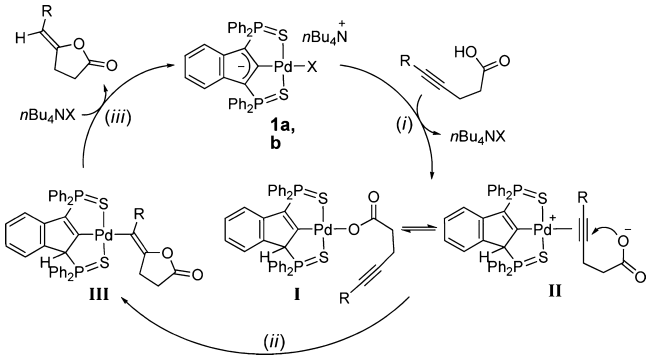
Scheme 1. Simplified Catalytic Cycle Proposed for the Cyclization of Alkynoic Acids Catalyzed by 1a,b



To try to gain some insight into the catalyst resting state, the cyclization of **4a** catalyzed by **1b** was monitored by NMR spectroscopy. During the course of the reaction, the ^{31}P NMR spectrum displays two broad signals around 60 ppm (see Supporting Information Figure S4).[13] Although these signals cannot be assigned unequivocally at this stage, they fall in the typical range for 2-indenyl complexes and can be tentatively attributed to complexes of type **I**–**III**. At the end of the reaction (as deduced from the complete conversion of **4a** into **5a** in the ^{1}H NMR spectrum), the ^{31}P NMR spectrum shows a unique sharp signal corresponding to the iodopalladate **1b**. These observations substantiate the noninnocent character of the indenediide backbone and support its participation in reversible proton transfer.

In conclusion, indenediide Pd pincer complexes **1a**–**c** stand as very efficient all-in-one catalysts for the cycloisomerization of alkynoic acids. They are competent toward a broad range of alkynoic acids, including functionalized and internal ones, and give access to 5- as well as 6- and 7-membered lactones with very high selectivities (in only 1 case over 13, a mixture of 5- and 6-membered rings was obtained) and in excellent yields (most often >95%). Protonation or methylation of the ligand backbone (2-indenyl Pd pincer complexes **2a** and **3a**,**b**) completely shut down the catalytic activity, indicating that the electron-rich indenediide backbone actively participates in the transformation.These results extend further the scope of metal–ligand cooperative catalysis and highlight its versatility and efficiency. To the best of our knowledge, there are only very few precedents of cooperative hydrofunctionalization reactions, and they all deal with intramolecular hydroamination reactions.[23] It is also striking to note that despite the prominent role of Pd in homogeneous catalysis, Pd complexes have not been involved in cooperative catalysis until very recently, and the results described herein represent only the second example in this area.[24]

■ ASSOCIATED CONTENT

Supporting Information

Experimental details and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(20) The 2-indenyl iodo palladium complex **2b** (R = H, X = I) is insoluble in $CDCl_3$, which hampers evaluation of its catalytic activity.

(21) Instead of iodine dissociation, the necessary vacant site at Pd may be generated by decoordination of one of the P═S sidearms. This is less likely but cannot be discarded at this stage.

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