How to cite: Angew. Chem. Int. Ed. 2024, e202406226
doi.org/10.1002/anie.202406226

Carbonylation

Palladium-Catalyzed Inward Isomerization Hydroaminocarbonylation of Alkenes

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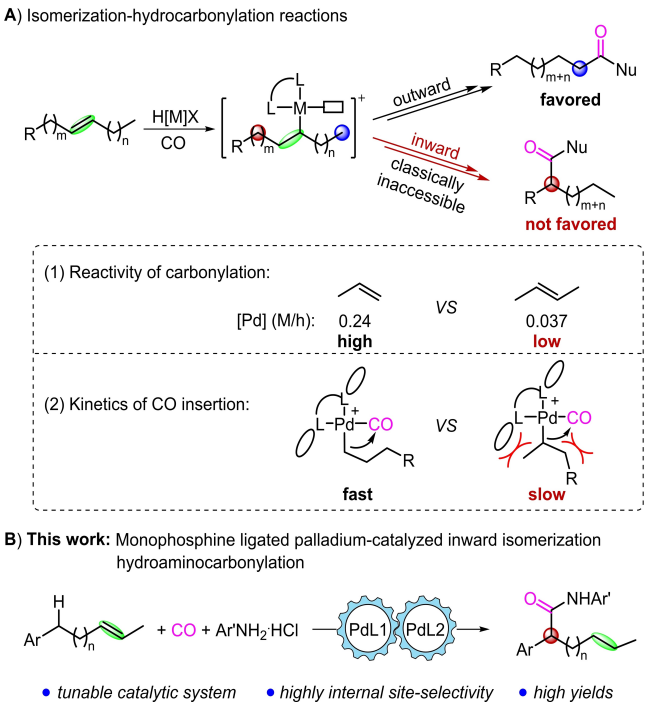
Abstract: In contrast to the kinetically favored outward isomerization-hydrocarbonylation of alkenes, the disfavored inward isomerization-hydrocarbonylation of alkenes remains an important challenge. Herein, we have developed a novel and effective palladium-catalyzed inward isomerization-hydroaminocarbonylation of unactivated alkenes and aniline hydrochlorides for the formation of synthetically valuable α-aryl carboxylic amides in high yields and high site-selectivities. The high efficiency of the reaction is attributed to a relay catalysis strategy, in which the Markovnikov-favored [PdH]-P^{t}Bu$_3$ catalyst is responsible for inward isomerization, while the [PdH]-Ruphos catalyst is responsible for hydroaminocarbonylation of the resulting conjugated aryl alkenes. The reaction exhibits highly functional group tolerance and provides a new method for formal carbonylation of remote C(sp^3)–H bond.

Isomerization-hydrocarbonylation of alkenes represents a fundamental important reaction in both organic synthesis and chemical industry. This is not only due to its utility in transforming unrefined isomeric mixtures of alkenes into a single value-added carbonyl-containing product, but also because of its high efficiency in the formal carbonylation of a remote C(sp^3)–H bond on alkene substrates.[1–3] For example, isomerization-hydroformylation of internal olefins has been widely utilized to access linear aldehydes,[1] and isomerization-hydrocarbonylation of plant oils has been developed for the synthesis of long-chain fatty dicarboxylic acids.[4] In general, the bidentate bisphosphine-transition-metal hydride complexes are involved as highly reactive catalysts in isomerization-hydrocarbonylation reactions, in which both hydrometallation and β-H elimination occur rapidly under a bulky and coordinatively unsaturated cationic catalyst.[5] However, despite of both terminal-selective (outward fashion) and internal-selective (inward fashion) isomerization-functionalization of alkenes, including isomerization-hydroalkyl(aryl)ation,[6,7] isomerization-hydroamination,[8] isomerization-hydrohalogenation[9] isomerization-hydroborylation,[10] isomerization-hydrosilylation[11] and isomerization-hydrocyanation[12] have recently been well developed, internal-site selective (inward fashion) isomerization-hydrocarbonylation reaction, which would provide a unique pathway to access synthetically valuable branched carbonyl compounds, remains challenging (Scheme 1A). The reasons for this challenging issue are attributed to: (1) the carbonylative reactivity of the internal alkene isomers is significantly lower than that of the terminal isomers,[13] (2) Markovnikov hydrocarbonylation is typically disfavored because the migratory insertion of CO into the sterically hindered secondary alkyl-[M] species is kinetically slower than that of primary alkyl-[M] intermediate.[14]

To achieve site selective inward isomerization-hydrocarbonylation, a catalyst that enables Markovnikov hydrometallation of terminal alkenes under a CO atmosphere is an important prerequisite, thus requiring a monophosphine ligated neutral palladium-hydride catalyst rather than the conventional bisphosphine ligated cationic ones.[15] Never-



Scheme 1. Palladium-catalyzed isomerization-hydrocarbonylation reaction.

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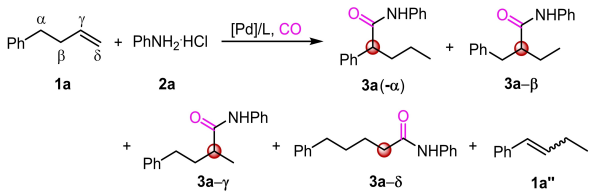
theless, due to the low reactivity of neutral palladium hydride catalyst in alkene isomerization, especially because the critical competition between carbonylation and isomerization on the same secondary alkyl-[Pd] species,[16] site-selective inward isomerization-hydrocarbonylation remains a daunting challenge in synthetic chemistry. Based on our interest in carbonylation reactions,[15a–c,17] we envisioned that the combination an isomerization-responsible catalyst along with a hydrocarbonylation-responsible catalyst might be a potential strategy to make the reaction feasible.[18–19] Herein, we present the development of a palladium-catalyzed inward isomerization-hydroaminocarbonylation of alkenes for the highly site-selective formation of α-aryl carboxylic amides (Scheme 1B).

Aiming to develop a novel palladium-catalyzed highly site-selective inward isomerization-hydrocarbonylation, we initiated our studies by using alkene **1a** and aniline hydrochloride **2a** as the substrates and conducted the reaction at 110 °C under a CO atmosphere (20 atm) in 1,4-dioxane (Table 1, entry 1). With traditional bisphosphines as the ligand, linear amide **3a-δ** was obtained as the predominant product as expected. In this context, various monodentate phosphine ligands were screened under the conditions.[15] Nevertheless, due to the competition between isomerization and carbonylation under these situations,[16,20] random isomerization-hydroaminocarbonylation were observed in the most cases (entries 2–8). After many attempts, we were delighted to find that highly site-selective isomerization-hydroaminocarbonylation occurred in the presence of $Pd(P^tBu_3)_2$ catalyst, but only a 23 % yield of **3a** was obtained, along with a 69 % yield of the isomerized byproduct **1a″** recovered (entry 9). Nevertheless, the yield of **3a** could not be further improved even by prolonging the reaction time or optimizing the parameters including solvents and temperatures (see Table S1 in Supporting Information).

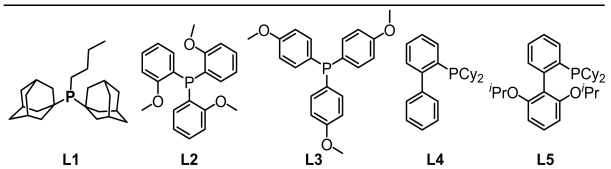
Considering that the sterically bulky $Pd(P^tBu_3)_2$ catalyst displays high reactivity in isomerization of alkenes but shows lower reactivity in carbonylation with CO and aniline, we hypothesized that the highly site-selective inward isomerization-hydrocarbonylation might be achieved through a relay catalysis strategy. As a result, additional palladium catalyst and phosphine ligand were introduced into the reaction. After several attempts, we were fortunate to find that the yield of **3a** was importantly improved using a dual-catalyst system consisting of $Pd(P^tBu_3)_2$ and $PdBr_2$/Ruphos (entry 11). Nevertheless, the isomerized byproduct **1a″** was still recovered in a 22 % yield. Since the pressure of CO typically plays an important role in a carbonylation reaction,[21] we then investigated the pressure effect of CO. As depicted in Scheme 2, with an increasing pressure of CO, the yield of **3a** was improved and the yield of isomerized byproduct **1a″** was decreased. Finally, it was found that 30 atm of CO is optimal. Under the conditions, an 86 % yield of the amide **3a** was obtained along with only trace of the site isomers (**3a-β**, **3a-γ** and **3a-δ**). Additionally, the palladium-catalyzed asymmetric isomerization-hydroaminocarbonylation using a chiral ligand has been studied, but only 17 % ee was achieved at the current stage (see Table S3, in Supporting Information).

With the optimized conditions in hand, the scope and limitations of this inward isomerization-hydroaminocarbonylation have been explored (Table 2). 4-Aryl-1-butenes with electron-donating groups on the aryl ring, such as alkyl, methoxyl, 1,3-dioxole, were tolerated under the conditions to afford the 2-arylpentanamide **3a**–**3h** in high yields (72 %–86 %) with excellent site-selectivities. 4-Aryl-1-butenes with various electron-withdrawing groups on the aryl ring, such

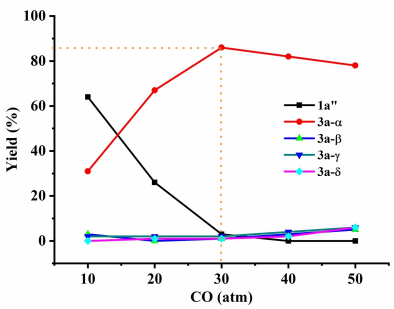
Table 1: Optimization of the reaction conditions.[a]



entry	[Pd]	ligand	yield (%)			
			3a	**3a**–β	**3a**–γ	**3a**–δ
1	$PdCl_2$	Xantphos	1	1	13	62
2	$PdCl_2$	PPh_3	1	4	40	14
3	$PdCl_2$	PCy_3	7	7	14	8
4	$PdCl_2$	L1	1	0	12	5
5	$PdCl_2$	L2	1	2	20	7
6	$PdCl_2$	L3	2	2	16	7
7	$PdCl_2$	L4	2	1	10	4
8	$PdCl_2$	L5	11	5	22	10
9	$Pd(P^tBu_3)_2$	--	23	0	1	0
10[b]	$Pd(P^tBu_3)_2$	$PdCl_2$/L5	54	0	5	1
11[b]	**$Pd(P^tBu_3)_2$**	**$PdBr_2$/L5**	68	0	2	1
12[b]	$Pd(P^tBu_3)_2$	PdI_2/L5	47	0	4	2



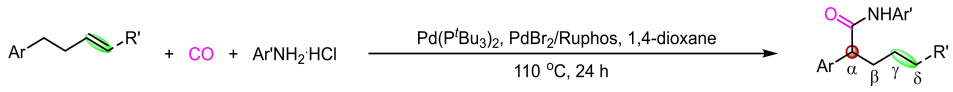
[a] Conditions: unless otherwise noted, 4-phenyl-1-butene **1a** (0.24 mmol), aniline hydrochloride **2a** (0.2 mmol), [Pd] (3 mol %), ligand (6 mol %), CO (20 atm), 1,4-dioxane (1.4 mL), 110 °C, 24 h, isolated yield. [b] PdX_2 (3 mol %), Ruphos (3 mol %) were added.



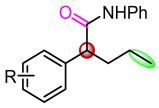
optimal conditions	
Comp.	yield (%)
1a"	3
3a-α	86
3a-β	<1
3a-γ	<1
3a-δ	<1

Scheme 2. The effect of CO pressure on the reaction.

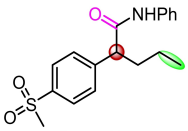
Table 2: Palladium-catalyzed isomerization hydroaminocarbonylation of unactivated alkenes with aniline hydrochlorides.[a]



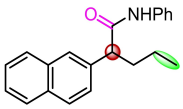
1 2 3, 4



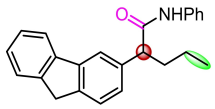
R = H **3a**, 86% yield, α : (β+γ+δ) = 96:4
R = 2-Me **3b**, 75% yield, α : (β+γ+δ) = 98:2
R = 3-Me **3c**, 72% yield, α : (β+γ+δ) > 99:1
R = 4-Me **3d**, 86% yield, α : (β+γ+δ) > 99:1
R = 3,5-di-Me **3e**, 85% yield, α : (β+γ+δ) = 98:2
R = 4-^{t}Bu **3f**, 82% yield, α : (β+γ+δ) > 99:1
R = 4-OMe **3g**, 78% yield, α : (β+γ+δ) > 99:1
R = 3,4-(OCH_2O) **3h**, 77% yield, α : (β+γ+δ) > 99:1
R = 4-F **3i**, 90% yield, α : (β+γ+δ) > 99:1
R = 4-Cl **3j**, 86% yield, α : (β+γ+δ) > 99:1
R = 4-Br **3k**, 87% yield, α : (β+γ+δ) = 98:2
R = 4-CF_3 **3l**, 75% yield, α : (β+γ+δ) = 95:5
R = 4-CO_2Me **3m**, 64% yield, α : (β+γ+δ)[b] > 99:1



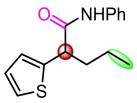
3n, 67% yield
α : (β+γ+δ)[b] = 89:11



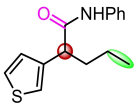
3o, 77% yield
α : (β+γ+δ) = 90:10



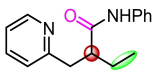
3p, 62% yield
α : (β+γ+δ) = 91:9



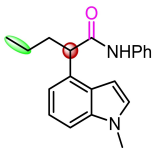
3q, 60% yield
α : (β+γ+δ) > 99:1



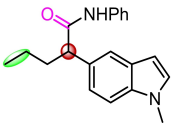
3r, 62% yield
α : (β+γ+δ) > 99:1



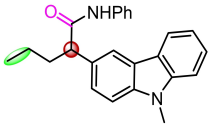
3s, 77% yield
β : (γ+δ) = 96:4



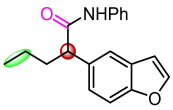
3t, 66% yield
α : (β+γ+δ) = 93:7



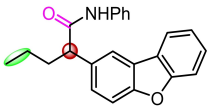
3u, 62% yield
α : (β+γ+δ) = 91:9



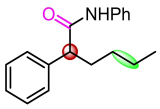
3v, 73% yield
α : (β+γ+δ) = 95:5



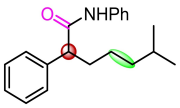
3w, 64% yield
α : (β+γ+δ) = 92:8



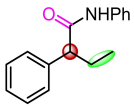
3x, 72% yield
α : (β+γ+δ) = 95:5



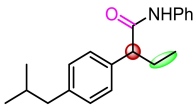
3y, 82% yield
α : (β+γ+δ) > 99:1



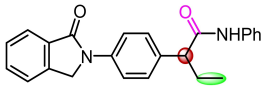
3z, 56% yield
α : (β+γ+δ) = 98:2



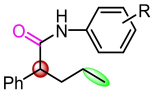
3aa, 88% yield
11β-HSD1 inhibitor precursor



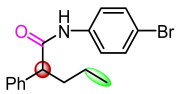
3ab, 86% yield
Butibufen precursor



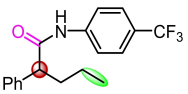
3ac, 72% yield
Indobufen precursor



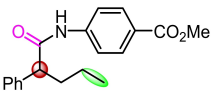
R = 4-Me **4a**, 72% yield, α : (β+γ+δ) > 99:1
R = 2-Me **4b**, 77% yield, α : (β+γ+δ) = 95 :5
R = 2-Ph **4c**, 84% yield, α : (β+γ+δ) > 99:1
R = 4-OMe **4d**, 65% yield, α : (β+γ+δ)[b] = 94:6
R = 4-OH **4e**, 61% yield, α : (β+γ+δ)[b] = 95:5
R = 4-F **4f**, 86% yield, α : (β+γ+δ) = 98:2
R = 4-Cl **4g**, 89% yield, α : (β+γ+δ) > 99:1
R = 2-Cl **4h**, 89% yield, α : (β+γ+δ) > 99:1
R = 2-Br **4i**, 72% yield, α : (β+γ+δ) > 99:1



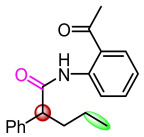
4j, 83% yield
α : (β+γ+δ) = 98:2



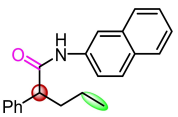
4k, 70% yield
α : (β+γ+δ) = 95:5



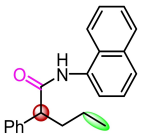
4l, 88% yield
α : (β+γ+δ)[b] = 95:5



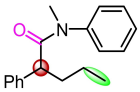
4m, 81% yield
α : (β+γ+δ) = 97:3



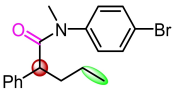
4n, 75% yield
α : (β+γ+δ) = 96:4



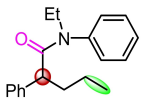
4o, 62% yield
α : (β+γ+δ) = 98:2



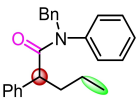
4p, 77% yield
α : (β+γ+δ) > 99:1



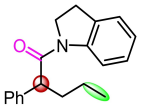
4q, 79% yield
α : (β+γ+δ) > 99:1



4r, 78% yield
α : (β+γ+δ) > 99:1



4s, 72% yield
α : (β+γ+δ) > 99:1



4t, 92% yield
α : (β+γ+δ) = 94:6

[a] Conditions: alkene **1** (0.24 mmol), Ar'NH_2·HCl **2** (0.2 mmol), CO (30 atm), Pd(P^tBu_3)$_2$ (3 mol%), $PdBr_2$ (3 mol%), Ruphos (3 mol%), 1,4-dioxane (1.4 mL), 110 °C for 24 h, isolated yield. α : (β+γ+δ) represents the ratio of the α-product to the sum of other isomers as determined by GC-MS analysis. [b] The ratio of α : (β+γ+δ) was determined by isolated yields of the isomers.

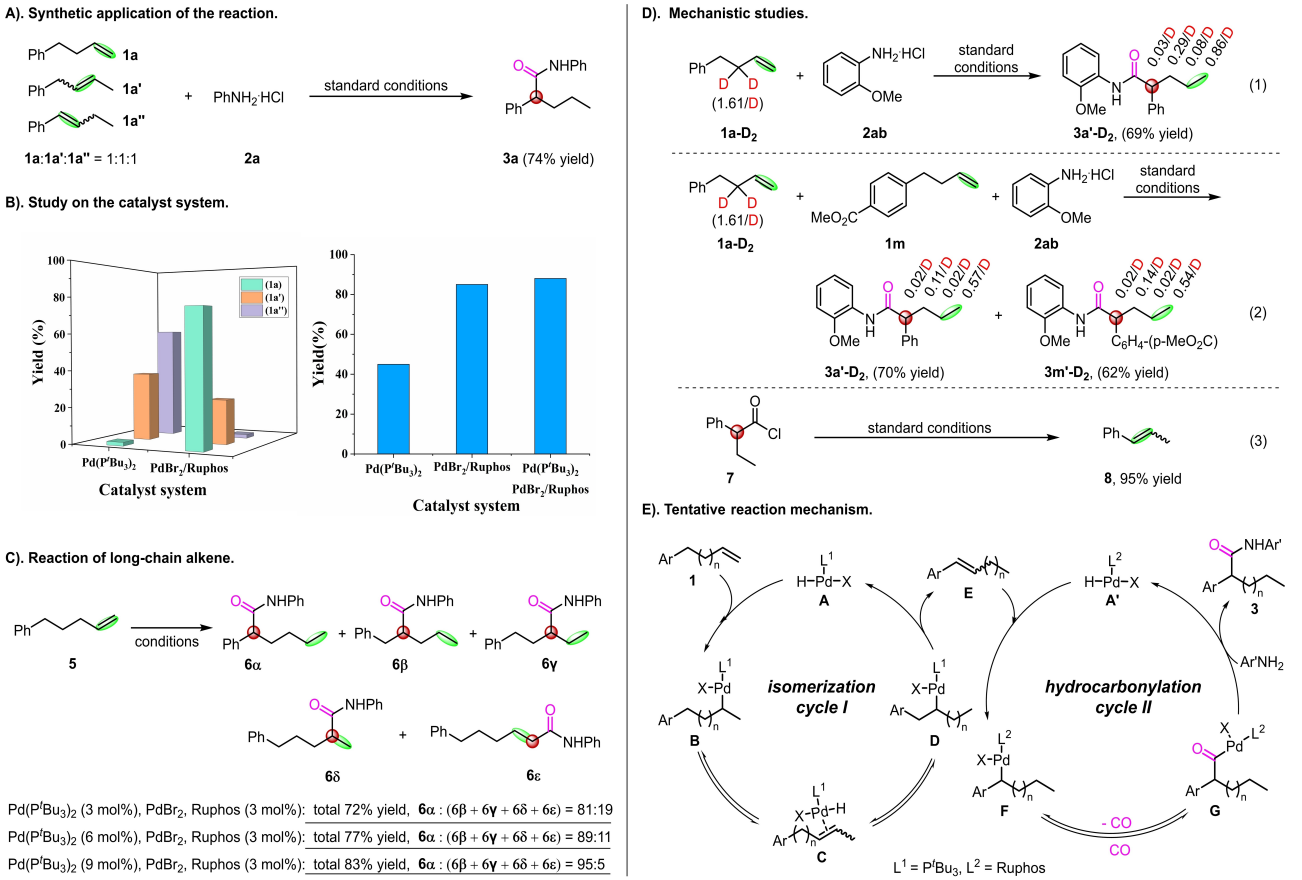
as fluoro, chloro, bromo, trifluoromethyl, methoxycarbonyl, and methylsulfonyl, were compatible with the conditions, giving rise to the corresponding 2-arylpentanamides **3i**–**3n** in good to high yields with highly site-selectivities. Notably, heterocycle-containing alkenes were feasible substrates in the reaction. With thiophene-containing, indole-containing,

carbazole-containing, benzofuran-containing and dibenzo-[*b*,*d*]furan-containing alkenes as the substrate, the corresponding isomerization-hydroaminocarbonylation products **3q**–**3r** and **3t**–**3x** were obtained in 60 % to 73 % yields and high site-selectivities. Exceptionally, with 2-(but-3-en-1-yl)pyridine as the substrate, the highly *β*-site selective product **3s** was obtained in 77 % yield, presumably because of the coordination effect of the pyridine group. In addition, unactivated internal alkenes (even in E/Z mixtures) were also tolerated in the reaction, forming the 2-phenylhexanamide **3y** and 6-methyl-2-phenylheptanamide **3z** in 82 % and 56 % yield, respectively. With allyl arenes as the substrates, the drug precursors **3ab** and **3ac**, which could be easily transformed into butibufen and indobufen, were obtained in 86 % and 72 % yield, respectively.

The scope and limitations of aniline substrates have been investigated (Table 2). The functional group tolerance on the aniline component is remarkable. Anilines with common functional groups including alkyl, methoxyl, fluoro, chloro, bromo, trifluoromethyl, methoxycarbonyl, and acetyl, were well compatible with the conditions, resulting in the corresponding 2-phenylpentanamides **4a**–**4m** in good to high yields. Owing to the stronger nucleophilicity of anilines than that of phenols, inward isomerization-hydroaminocarbonylation of 4-aminophenol occurred chemoselectively and site-selectively to afford the corresponding amide **4e** in a 61 % yield. Notably, the electron-deficient anilines show slightly higher site-selectivity than electron-rich ones. Similarly, when steric hindered anilines such as 2-methylaniline, 2-phenylaniline, 2-chloroaniline, 2-bromoaniline, 1-naphthylamine and secondary anilines was used as the substrate, high to excellent site-selectivity was obtained. Nevertheless, the aliphatic amine hydrochloride salts, such as benzylamine hydrochloride and butan-1-amine hydrochloride, could not be tolerated in the reaction.

Furthermore, to demonstrate the usefulness of this inward isomerization-hydroaminocarbonylation, the unrefined isomeric mixtures of alkenes were subjected to the reaction (Scheme 3A). Delightfully, 2-phenylpentanamide **3a** was obtained in 74 % yield.

To gain insight into the mechanism, the respective roles of the $Pd(P^tBu_3)_2$ and $PdBr_2$/Ruphos catalysts have been studied in the absence of aniline substrate. As depicted in Scheme 3B, $Pd(P^tBu_3)_2$ shows higher reactivity than that of the $PdBr_2$/Ruphos catalyst in the isomerization of the alkene **1a**. In contrast, the $PdBr_2$/Ruphos catalyst shows higher efficiency than that of the $Pd(P^tBu_3)_2$ catalyst in the carbonylation of the internal alkene **1a**″. These results suggest that the $Pd(P^tBu_3)_2$ catalyst is probably responsible for the isomerization of the alkenes, while the $PdBr_2$/Ruphos catalyst is mainly responsible for the hydroaminocarbonylation of the resulting internal alkenes. Therefore, when long-



Scheme 3. Reaction studies. A). Synthetic application of the reaction. B). Study on the catalyst system. C). Reaction of long-chain alkene. D). Mechanistic studies. E). Tentative reaction mechanism.

chain alkenes are involved in the reaction, we could adjust the reactivity and site-selectivity of the reaction by tuning the loading of the corresponding catalysts. This is a distinct advantage of this method. For example, the reactivity and site-selectivity of the reaction of the long-chain alkene **5** could be easily improved from a 72 % yield and 81 % α-site selectivity to an 83 % yield and 95 % α-site selectivity by increasing the loading of the isomerization-responsible catalyst $Pd(P^tBu_3)_2$ (Scheme 3C).

To gain further insight into the mechanism, deuterium-labeling experiments have been carried out under the standard conditions. Palladium-catalyzed isomerization hydroaminocarbonylation of deuterium-labeling alkene **1a-D$_2$** and 2-methoxylaniline hydrochloride produced 2-arylpentanamide **3a′-D$_2$** in a 69 % yield with deuterium distributed in the carbon chain (Scheme 3D(1)). This result suggested that the 1,2-hydride-shift type isomerization,[22] namely hydropalladation of alkenes and β-hydride elimination of the resulting alkyl-[Pd] species, proceeded rapidly under the conditions. The high deuterium distribution on β- and δ-position of **3a′-D$_2$** also indicated that our catalyst system favors Markovnikov hydropalladation, which probably provided the driving-force for inward isomerization.

Moreover, the intermolecular deuterium-exchange experiment suggested that the dissociation of the palladium-hydride (probably P^tBu_3-ligated [PdH] species) from the alkenes occurred rapidly,[23] ensuring that the following hydroaminocarbonylation proceeded well under the Ruphos-ligated [PdH] catalyst (Scheme 3D(2)). Furthermore, a control experiment using acid chloride **7** as the substrate has also been conducted under the standard conditions (Scheme 3D(3)). The decarbonylation of acid chloride **7** in the absence of aniline hydrochloride revealed that the insertion step of CO is likely reversible.[24]

Based on above experimental results, a tentative mechanism is proposed in Scheme 3E. The P^tBu_3-ligated [PdH] species is responsible for the inward isomerization of the terminal and internal alkenes to form the conjugated aryl alkenes, with the driving force of favored Markovnikov hydropalladation (cycle I). Subsequently, coordination and Markovnikov hydropalladation of the resulting aryl alkenes with the Ruphos-ligated [PdH] catalyst produces the alkyl-[Pd] intermediate **F** (cycle II). The alkyl-[Pd] **F** undergoes CO coordination and insertion to give the acyl-[Pd] intermediate **G**. Finally, aminolysis of the acyl-[Pd] **G** generates the 2-aryl carboxylic amide **3**. In these catalytic cycles, the steps of isomerization and CO insertion are likely reversible.

In summary, we have developed a novel palladium-catalyzed inward isomerization-hydroaminocarbonylation of unactivated terminal/internal alkenes and aniline hydrochlorides for the formation of α-aryl carboxylic amides. The success of the process relies on the combination of a Markovnikov favored isomerization-active [PdH]-P^tBu_3 catalyst and a hydroaminocarbonylation-active [PdH]-Ruphos catalyst in the reaction. The adjustable loading of the individual catalyst ensures high efficiency for the reaction of long-chain alkenes. The reaction tolerates a wide range of functional groups and provides a new opportunity for the carbonylation of remote secondary C(sp^3)–H bond in high yields and high site-selectivity. Further scope and mechanistic studies of such reactions are currently underway in our laboratory.

Acknowledgements

This work was supported by generous grants from the National Natural Science Foundation of China (NSFC-22171224, 21971204) and the Innovation Capability Support Program of Shaanxi Province (No. 2020TD-022).

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

Keywords: palladium catalysis · carbon monoxide · isomerization-hydrocarbonylation · amide formation · sp3 C–H bond carbonylation

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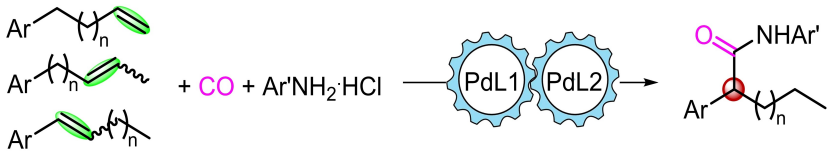
Manuscript received: April 1, 2024
Accepted manuscript online: April 15, 2024
Version of record online: ■■, ■■

Communications

Carbonylation

X.-J. Zou, Z.-X. Jin, H.-Y. Yang, F. Wu, Z.-H. Ren, Z.-H. Guan* e202406226

Palladium-Catalyzed Inward Isomerization Hydroaminocarbonylation of Alkenes



- *tunable catalytic system*
- *highly internal site-selectivity*
- *high yields*

A novel palladium-catalyzed inward isomerization and hydraminocarbonylation of unactivated alkenes for the synthesis of α-aryl carboxylic amides has been developed. The combination isomerization-responsible catalyst and hydrocarbonylation-responsible catalyst was found to be a highly effective strategy to render the reaction feasible. The reaction shows highly functional group compatibility and site-selectivity.