DOI: 10.1002/ejoc.200700369

Palladium-Catalyzed C–N Bond Activation: The Synthesis of β-Amino Acid Derivatives from Triethylamine and Acrylates

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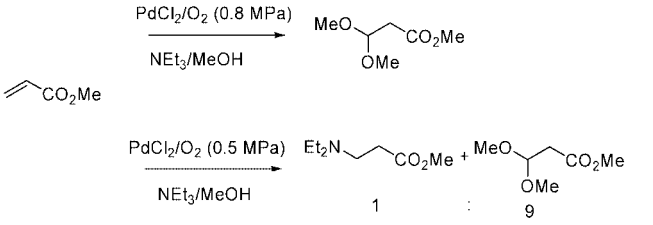
Keywords: Palladium / C–N bond activation / Amino acids

In the palladium-catalyzed reaction of acrylates, C–N bond activation and acetalization occurred under different conditions. Described herein is a highly efficient palladium-catalyzed C–N bond activation reaction and subsequent new C–N bond formation to directly construct β-amino acids from triethylamine and acrylate esters in isolated yields of up to 95 %.

Introduction

Palladium-catalyzed processes have proven to be a powerful and useful tool for the synthesis of nitrogen-containing organic molecules in synthetic organic chemistry.[1] Palladium is able to effect an extraordinary number of very different reactions, including C–H or C–C activation reactions in the presence of a nitrogen-containing functional groups. Recent work has focused on Pd-catalyzed C–N bond formation;[2] however, considerably less attention has been devoted to the Pd-catalyzed C–N bond activation of alkylamines,[3] which might provide an alternative to traditional functional group organic chemistry. In previous work,[4] triethylamine was employed as the base in the Pd-catalyzed acetalization reaction of methyl acrylate with methanol. If the amount of molecular oxygen is not sufficient,[4d] the cleavage of the C–N bond in ethylamine occurs and a small amount of methyl 3-diethylaminopropionate, a β-amino acid ester, can be detected in the reaction mixture [Equation (1)]. With the aim to seek novel and highly efficient synthetic approaches, a new route to construct β-amino acid esters through C–N bond cleavage of trialkylamines and subsequent new C–N bond formation is worthy of study.

The synthesis of β-amino acids and their derivatives is of great interest in industrial and academic research for medicinal and organic synthetic chemists, because β-amino acid derivatives have the potential to be biologically active and have medicinal value;[5] they can also serve as highly versatile building blocks in synthetic organic chemistry. In recent years, the development of β-amino acid derivatives has provided new protocols. Shen discovered that a kind of β-amino acid with pyrazole showed good vitro antiviral activity against HIV-1.[6] Wani and Tarlor isolated methyl (2*R*,3*S*)-*N*-benzoyl-3-phehylisoserine, which displays significant cytotoxicity.[7] Several important methods have been developed for the synthesis of β-amino acid derivatives.[8] Herein we report a new type of synthesis for β-amino acid derivatives through Pd-catalyzed C–N bond activation of trialkylamine and subsequent addition to acrylate esters under mild conditions.



(1)

Results and Discussion

$PdCl_2$ Catalysis in Supercritical Carbon Dioxide

It is well-known that supercritical carbon dioxide ($scCO_2$) is an important and attractive organic reaction media in green chemistry research.[9–10] According to the experimental operation in $scCO_2$,[4] when triethylamine (**1a**) and methyl acrylate (**2a**) were induced in the palladium chloride catalytic system in the absence of O_2, methyl 3-diethylaminopropionate (**3a**) was obtained as the sole prod-

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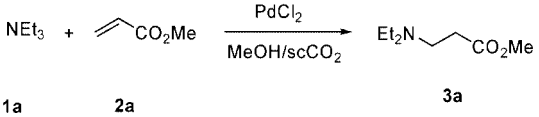
uct [Equation (2)]. This result indicated that β-amino acids could be directly constructed from triethylamine and acrylate esters.



1a 2a 3a (2)

It is necessary to add an appropriate dosage of HOAc to accomplish the reaction; otherwise, the reaction exhausts the stoichiometric dosage of $PdCl_2$. When the dosage of HOAc is increased from 0.5 equiv. to 1.5 equiv. (based on the amount of **2**), the yield of **3a** increased. However, when the dosage of HOAc exceeded 1.5 equiv., the yield of **3a** decreased and *N*,*N*-diethylacetamide was detected. Thus, the suitable dosage of HOAc was 1.0 equiv. on the basis of the amount of substrate used.

The results of the $PdCl_2$-catalyzed reaction in a series of CO_2 pressure is summarized in Table 1. As the reaction pressure was increased from 9 to 20 MPa, the yield increased from 80 to 95% (Table 1, Entries 1–4). Higher pressure, such as 30 MPa, does not raise the yield any further (Table 1, Entry 5). The results indicate that: (1) $scCO_2$ is a suitable solvent for the $PdCl_2$-catalyzed reaction of triethylamine with methyl acrylate and (2) the pressure could affect the chemical equilibrium, the chemical reaction rate and the catalytic activity.[11]

Table 1. $PdCl_2$-catalyzed reaction of triethylamine with methyl acrylate in $scCO_2$.[a]

Entry	Reaction pressure [MPa]	Additive	Yield[b] [%]
1	9	MeOH	80
2	10	MeOH	80
3	15	MeOH	92
4	20	MeOH	95
5	30	MeOH	95
6	15	none	72
7	15	EtOH	26
8	15	H_2O	–

[a] Reaction conditions: molar ratio of triethylamine/methyl acrylate/HOAc, 2.0:1.0:1.0, 3 mol-% $PdCl_2$, 48 h, 70 °C. [b] Isolated yield.

Most organometallic or transition metals are difficult to dissolve in $scCO_2$.[12] To improve the solubility in $scCO_2$, some organic or inorganic compounds, so-called "modifiers", can be added to the solution.[13] Among these extremely effective modifiers, MeOH is one of the most common. Our group used MeOH to promote the partial dissolution of $PdCl_2$ in $scCO_2$ and developed a series of organic reactions in $scCO_2$.[4,14] Besides MeOH, other solute modifiers could be used to promote dissolution of $PdCl_2$ in $scCO_2$. Table 1 also gathers the reaction results in the presence of different kinds of solute modifiers. In the absence of MeOH, reactions of triethylamine with terminal olefins gave a moderate yield of 72% (Table 1, Entry 6). The addition of MeOH raised the reaction yield to 92% (Table 1, Entry 3). when methanol was replaced by ethanol, the yield dropped to 26% (Table 1, Entry 7). If water was used as the solute modifier, the reaction does not occur. So MeOH was shown to be the best modifier to promote the reaction (Table 1, Entry 8).

$PdCl_2$ Catalysis in Conventional Solvents

Various conventional solvents were investigated in this reaction as shown in Table 2. With the use of the optimum mole ratio of triethylamine/methyl acrylate/HOAc, the different organic solvents could be employed in most cases. DMF, THF and CH_3CN are better solvents than dioxane, toluene, HMPA and NEt_3. In DMF, THF and CH_3CN, the reaction could be carried out smoothly with 86, 89 and 90% yields, respectively (Table 2, Entries 1–3). By using water as the solvent, no methyl 3-diethylaminopropionate was detected (Table 2, Entry 8).

Table 2. $PdCl_2$-catalyzed reaction of triethylamine with methyl acrylate in conventional solvents.[a]

Entry	Solvent	Yield[b] [%]
1	DMF	86
2	THF	89
3	CH_3CN	90
4	Dioxane	73
5	Toluene	37
6	HMPA	33
7	NEt_3	38
8	H_2O	–

[a] Reaction conditions: molar ratio of triethylamine (**1a**)/methyl acrylate (**2a**)/HOAc, 2.0:1.0:1.0, 3 mol-% $PdCl_2$, 48 h, 70 °C. [b] Isolated yield.

Different Olefins

Different functionalized olefins were subjected to the reaction under the optimized conditions. Representative examples are tabulated in Table 3. Substrates ethyl acrylate

Table 3. $PdCl_2$-catalyzed reaction of triethylamine with different olefins.[a]

Entry	Substrate	Product	Solvent	Yield[c] [%]
1	**2a**	**3a**	$scCO_2$[b]	92
2	**2b**	**3b**	$scCO_2$[b]	84
3	**2b**	**3b**	DMF	95
4	**2b**	**3b**	THF	56
5	**2c**	**3c**	$scCO_2$[b]	75
6	**2c**	**3c**	THF	69
7	**2d**	**3d**	$scCO_2$[b]	82
8	**2d**	**3d**	THF	20
9	**2e**	**3e**	$scCO_2$[b]	53
10	**2e**	**3e**	THF	59
11	**2f**	**3f**	$scCO_2$[b]	–
12	**2g**	**3g**	$scCO_2$[b]	–

[a] Reaction conditions: molar ratio of triethylamine (**1a**)/substrate **2**/HOAc, 2.0:1.0:1.0, 3 mol-% $PdCl_2$, 48 h, 70 °C. [b] The total reaction pressure was 15 MPa and 2 mL of methanol was added. [c] Isolated yield.

(**2b**) and *n*-butyl acrylate (**2c**) gave the corresponding β-amino acid esters **3b** and **3c**, respectively, in moderate-to-excellent yields in $scCO_2$, DMF and THF (Table 3, Entries 2–6). Acrylonitrile (**2d**) and acrylamide (**2e**), the nitrogen-containing derivatives of acrylate, could also react with triethylamine to give 3-diethylaminopropionitrile (**3d**) and 3-diethylaminopropionamide (**3e**), respectively, with moderate yields in different solvents (Table 3, Entries 7–10). Methyl but-2-enoate (**2f**), acrylate substituted in the 3-position, did not react with triethylamine (Table 3, Entry 11), because of the steric repulsion of the methyl group on the carbon–carbon double bond. Styrene (**2g**; Table 3, Entry 12) did not react with triethylamine, because the electron-donating group of styrene cannot stabilize the carbanion, and the protonolysis reaction cannot occur.[15]

The Mechanistic Study

In our catalytic reactions, it is notable that the desired processes proceeded in the presence of HOAc and in the absence of molecular oxygen. This revealed that HOAc and molecular oxygen play important roles in the $PdCl_2$-catalyzed C–N activation and then C–N bond formation sequence.

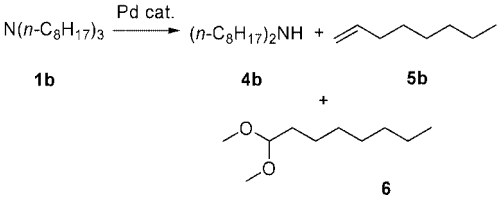
In the $PdCl_2$-catalyzed acetalization, the presence of HOAc is not necessary to accomplish the reaction. However, the addition of HOAc is necessary in the $PdCl_2$-catalyzed reaction of triethylamine with acrylate; if not, the substrates will remain or the stoichiometric dosage of $PdCl_2$ will be exhausted. When 0.5–1.5 equiv. of HOAc was added to the reaction mixture, with the use of only a catalytic amount of $PdCl_2$ (3 mol-%), the reaction could be smoothly carried out, and it is notable that no reaction occurred in the absence of $PdCl_2$. The results indicate that: (1) a catalytic amount of $PdCl_2$ led to C–N bond cleavage and (2) the role of HOAc might be to regenerate the active palladium species through β-hydrogen elimination or protonolysis,[15] which led to completion of the reaction.

The oxidant is another key factor for the $PdCl_2$-catalyzed reaction. When the oxidant, such as $CuCl_2$, benzoquinone or molecular oxygen, is part of the reaction mixture, the reaction gave acetal as the sole product.[4] When the oxidant is absent, methyl 3-diethylaminopropionate was obtained as the sole product. We also found that the mixture of acetal and β-amino acid ester was detected when the amount of molecular oxygen was not enough.[4d] Therefore, the presence of the oxidant resulted in different reaction pathways. According to the explanation of previous work, the mechanism of acetalization proceeds by a Pd^{II}-induced intramolecular oxypalladation of the alkene.[4c,16] In the absence of an oxidant, Pd^{II} complexes abstract a hydrogen atom from the alkyl group of the amine.

The cleavage of the C–N bond of NEt_3 is of focus in the study of the mechanism. Hosokawa believed that the oxidative cleavage of the C–N bond occurred by a I–Pd–OOH species.[3a] The I–Pd–OOH species was derived from either I–Pd–H and O_2 or peroxidopalladium(II) and HI. Then, dealkylation of NEt_3 occurred by the oxidation of the I–Pd–OOH species. The ethyl group that is removed from NEt_3 must be transformed into MeCOOH by MeCHO. The $NHEt_2$ that is formed further reacts with methyl acrylate to give (diethylamino)propionate. It is notable that if in the presence of molecular oxygen, the reaction gives (diethylamino)propionate. Once argon replaces molecular oxygen, no (diethylamino)propionate is detected. Ziolkowski proposed another way of C–N bond cleavage, which was induced by the water in the reaction system.[3b] The reaction starts with the activation of the C–H bonds of the amine that are coordinated to palladium and the formation of the Pd–C bond. The next step consists of nucleophilic attack of OH (from water) on the α carbon of the intermediate complex followed by the rearrangement to the aldehyde and secondary amine. The proposed reaction pathway is close to the mechanism of the Wacker process.

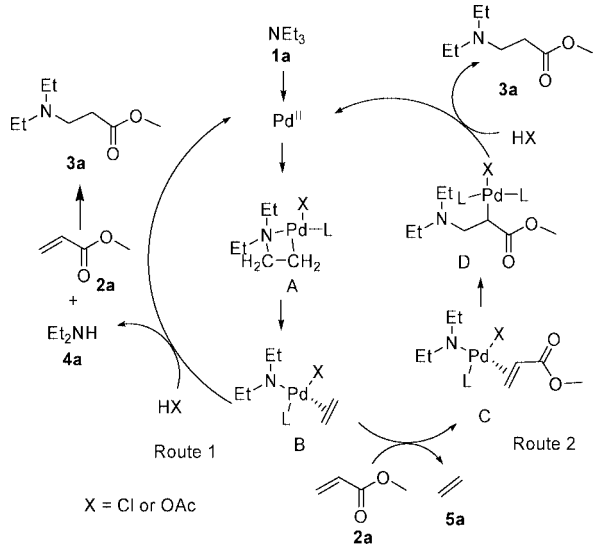
Neither Hosokawa's mechanism nor Ziolkowski's hypothesis could totally reasonably explain the phenomena in our experimental results. The existence of O_2 or water is unfavourable for the production of diethylaminopropionate.

To clarify the C–N bond-cleavage mechanism, we choose tri-*n*-octylamine (**1b**) as a replacement for triethylamine [Equation (3)], and we hoped to capture the intermediates. Fortunately, the reaction was carried out under standard conditions, and dioctylamine (**4b**), octylene (**5b**) and octylene acetal (**6**) were all detected. The results hinted that: (1) in the absence of molecular oxygen and water, the C–N bond cleavage still proceeds in palladium catalysis and (2) β-hydrogen elimination exists in the Pd^{II}-catalyzed C–N bond-cleavage process.



(3)

The reaction pathway depicted in Scheme 1 might accommodate all the above results. The C–H bond of triethylamine that is coordinated to palladium is initially activated, and the Pd–C bond can form. Then, C–N bond cleavage occurs to give intermediate B. Methyl (diethylamino)-propionate (**3a**) might be obtained by route 1 or route 2. From route 1, by the action of acid, intermediate B splits into the activated Pd^{II} species and diethylamine (**4a**). Compound **4a** can further react with **2a** to give **3a**.[3b,17] From route 2, the exchange of ethylene in intermediate B with **2a** forms intermediate C. The insertion of the carbon–carbon double bond to the Pd–N bond affords intermediate D, and subsequently the C–Pd bond can be quenched by protonolysis to afford **3a**.[15] The activated Pd^{II} species can then be regenerated and brought into a new catalytic cycle.



Scheme 1.

Conclusions

The palladium-catalyzed C–N bond activation and subsequent new C–N bond formation, which was illustrated with the reaction of terminal olefins with electron-withdrawing groups, such as acrylate esters, acrylonitrile and acrylamide, could be carried out smoothly with efficiency. This methodology will provide the simplest and most effective way to construct β-amino acids and their derivatives.

Experimental Section

General: ^{1}H NMR spectra were recorded with a Bruker DRX-400 spectrometer with TMS as an internal standard. GC analyses were performed with a GC-930 chromatograph (Shanghai Haixian Chromatograph Instrument Ltd. Co.) with a flame ionization detector equipped with an OV-101 capillary column (internal diameter = 0.25 mm, length = 30 m). Mass spectra were recorded with a Shimadzu GC-MS-QP5050A at an ionization voltage of 70 eV equipped with a DB-WAX capillary column (internal diameter = 0.25 mm, length = 30 m). IR spectra were recorded with an Analect RFX-65A spectrometer. All acrylate esters, acrylonitrile, styrene, acrylamide, methyl but-2-enoate, methanol, ethanol, palladium chloride, acetone and acetic acid etc., were commercially purchased and used without further purification.

Typical Procedure for the $PdCl_2$-Catalyzed Reaction of Triethylamine and Methyl Acrylate in $scCO_2$: All reactions were carried out in a HF–25 autoclave. The $PdCl_2$ catalyst (0.15 mmol, 3 mol-%), MeOH (2 mL), triethylamine (10 mmol), acetic acid (5 mmol) and methyl acrylate (5 mmol) were added into a 25-mL autoclave in sequence. Liquid CO_2 was pumped into the autoclave by using a cooling pump to reach the desired pressure; the autoclave was then put into an oil bath under magnetic stirring for the desired reaction time. After completion of the reaction, the autoclave was cooled to –30 °C. CO_2 was vented and the surplus was extracted with *n*-hexane or petroleum ether. The extract was filtered and condensed under reduced pressure. The product was analyzed by GC (quantitative) and GC–MS, ^{1}H NMR and IR spectroscopic analysis (identification of products, some were purified by preparative TLC on silica gel by using light petroleum ether/ethyl acetate as the eluent before ^{1}H NMR and IR spectroscopy).

Supporting Information (see footnote on the first page of this article): Analytical and spectral data for compounds **3a**–**e**.

Acknowledgments

The authors thank the National Natural Science Foundation of China (Nos. 20332030, 20572027 and 20625205) for financial support of this work.

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Received: April 24, 2007
Published Online: July 19, 2007

