

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

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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

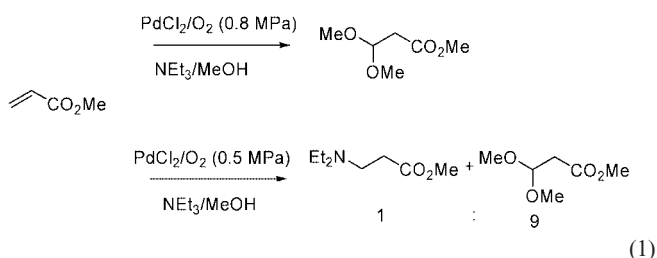
triethylamine and acrylate esters in isolated yields of up to 95 %.

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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 versa-



tile 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-phenylisoserine, 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.

Results and Discussion

PdCl₂ Catalysis in Supercritical Carbon Dioxide

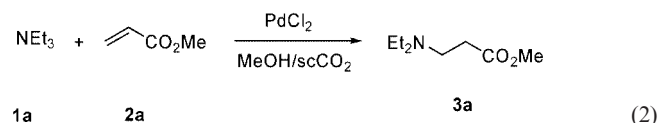
It is well-known that supercritical carbon dioxide (scCO₂) is an important and attractive organic reaction media in green chemistry research.^[9–10] According to the experimental operation in scCO₂,^[4] when triethylamine (**1a**) and methyl acrylate (**2a**) were induced in the palladium chloride catalytic system in the absence of O₂, 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.



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

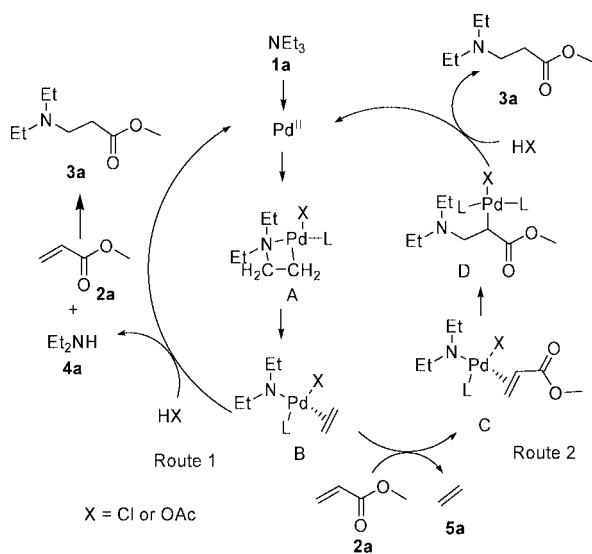
Different functionalized olefins were subjected to the reaction under the optimized conditions. Representative examples are tabulated in Table 3. Substrates ethyl acrylate

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.

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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: ^1H 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, ^1H NMR and IR spectroscopic analysis (iden-

tification of products, some were purified by preparative TLC on silica gel by using light petroleum ether/ethyl acetate as the eluent before ^1H NMR and IR spectroscopy).

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

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