A New Palladium Catalytic System of Heck Coupling Reaction for the Synthesis of Cinnamamide

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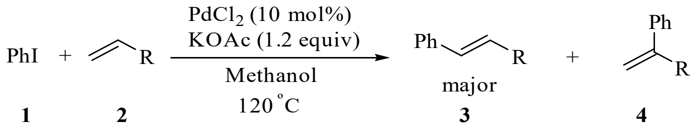
Abstract:
This work introduces a new palladium catalyst based on Methyl (*Z*)-(4-oxopent-2-en-2-yl)glycinate as multi-dentate ligand and its utilization in the Heck-Mizoroki coupling reaction between acrylamide as an electron deficient alkene and iodobenzene as example of aryl halide to form the corresponding cinnamamide in good to excellent yields. The highest turnover number (TON) and turnover frequency (TOF) of the catalytic system of this reaction were reached to 7067 and 1413, respectively.

Keywords: Heck Coupling Reaction, Schiff base, Catalyst, Cinnamamide, Acrylamide.

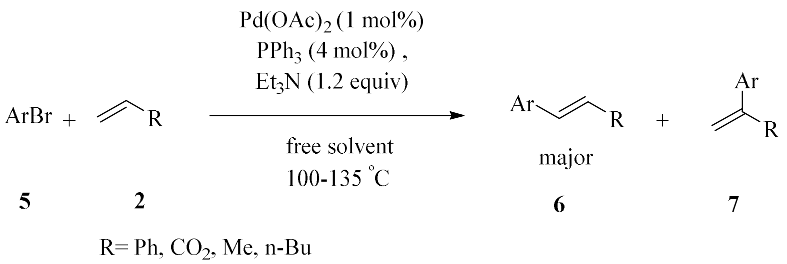
Introduction

Most industrial syntheses and nearly all biological reactions require catalysts [1], and the palladium-catalyzed cross-coupling reactions particularly Heck reaction have great significance for both academic, industrial research and in the production of a number of compounds on a large industrial scale and fine chemicals including pharmaceuticals, agricultural chemicals, and high-tech materials [2]. The Heck–Mizoroki reaction involves palladium-catalyzed coupling of an alkene with an alkenyl or aryl halide, leading to a substituted alkene [3]. It is also known *β*-stereospecific as the migratory insertion of the palladium complex into the olefin and the β-hydride elimination both proceed with *syn* stereochemistry [4]. This reaction is one of the most powerful methods for the formation of C-C bond. In 1971, Mizoroki *et al.* reported preliminary results on the $PdCl_2$-catalysed arylation of alkenes by iodobenzene in the presence of potassium acetate as base **(Scheme 1)**.



Scheme 1

Later, in 1974, Dieck and Heck developed the use of PPh_3 in association with $Pd(OAc)_2$ in presence of Et_3N **(Scheme 2)** [5], and from that period the improvement of this reaction attracted many researchers to develop more efficient catalytic system, less temperature or enhancing the yield.



Scheme 2

3-Phenylacrylamide or cinnamamide (**8**) constitutes an interesting scaffold within medicinal chemistry[6], cinnamamide derivatives were reported to have many different biological activities such as anti-cancer, anti-mitotic, anti-oxidant and seed-germination inhibitory effects [7-9] , and some of the cinnamamide derivatives exhibit a variety of biological activities. Amide (**9**) is an example of secondary metabolites isolated from the genus *piperaceae* which have been widely studied due to the biological properties of these plants [10], and *N*-(2-hydroxy ethyl) cinnamamide (**10**) was also found to possess a good anti-convulsant activity with low toxicity **(Figure 1)** [11].

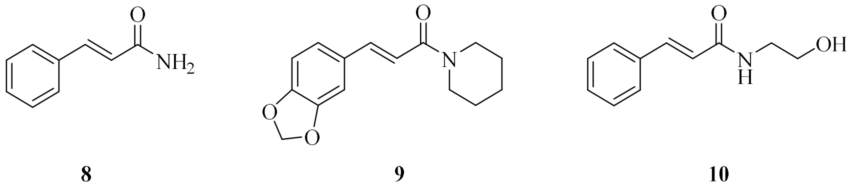
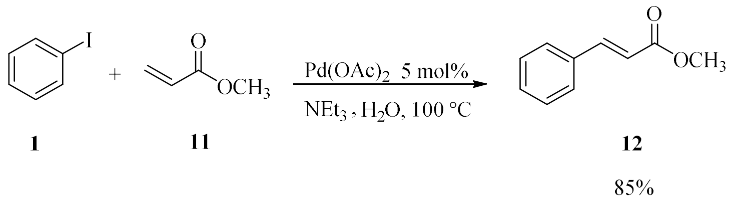


Figure 1

There are previous efforts for the synthesis of cinnamoyl system by coupling reaction between methyl acrylate (**11**) and iodobenzene (**1**). Herein, methyl cinnamate (**12**) was prepared according to the following heck reaction conditions; the yield was excellent **(Scheme 3)** [12].



Scheme 3

Applying Heck reaction for the synthesis of cinnamamide, starting from the acrylamide and introducing a new catalytic system for this reaction seem to be an attractive idea. Furthermore, evaluation the efficiency of the obtained catalyst.

Material and Methods

General

Starting materials and solvents were purchased from common commercial sources. All melting points were uncorrected. All R_f values were obtained by using GF_{254} TLC, on pre-coated silica plates. The UV spectrophotometer was used Cary 60 UV-Vis, Agilent Technologies with wavelength range (λ_{max} 190-1100 nm). Infrared spectra were measured on a Perkin Elmer Paragon RX I FT-IR spectrophotometer accompanied with ATR accessory. The ^{1}HNMR spectral data was registered on JEOL ECA500II (500 MHz) NMR spectrometer, making a solution of samples in $CDCl_3$, DMSO-*d₆* or $D_2O/CDCl_3$ solvents using the nmr standard absorption of these solvents as a references. MS spectral data were obtained using a Shimadzu Qp-2010 ples GC/mass spectrometer and MS spectra were recorded using EI at 70 eV.

Purification of some materials

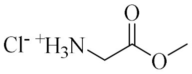
Aniline was distilled under reduced pressure from brown liquid to pale yellow at 102 °C/140 mmHg. Acetyl-acetone washed with diluted Na_2CO_3 to remove the traces of acetic acid, and then H_2O, after that distilled under reduced pressure, dried over Na_2SO_4 and filtered.

HPLC Conditions

The separation carried out by using the German-made HPLC (KNAUER), managed by Ezchrome Version 3.1.7.11, with reversed phase column Eurospher 100-5, C_{18}, 150 mm length and 4 mm radius. After various attempts, the recommended optimum HPLC conditions provided a good isolation were as follows: the mobile phase used was a mixture of acetonitrile and water in a ratio 3:7, respectively, ambient temperature, flow rate 1 mL/min; the wavelength of the UV detector was adjusted at 254 nm, and the injection volume per sample is 20 μL.

Synthesis of methyl glycinate hydrochloride (13) [13]

In **500** cm^3 three-necked RBF, acetyl chloride gradually (46 cm^3, 647 mmol) was dissolved gradually in MeOH (200 cm^3) using dropping funel. Glycine (17.12 g, 228 mmol) was then added to the solution and the reaction mixture was refluxed for 2 hrs. The solvent was removed under reduced pressure to give the crude product, which recrystallized from EtOH.

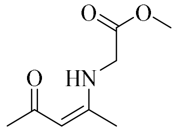


13

Product obtained as white solid (25 g, 87%). mp. 116-120 °C. IR (cm^{-1})**:** 2883**-**2686 (N—H), 1744 (C=O) ester.

Synthesis of Methyl (*Z*)-(4-oxopent-2-en-2-yl)glycinate (14) [14]

In 25 cm^3 RBF, methyl glycinate hydrochloride (3.26 g, 26 mmol) and Et_3N (3.62 cm^3, 26 mmol) were carefully added to a solution of the acetylacetone (2.6 cm^3, 26 mmol) in EtOH (50 cm^3). The mixture was stirred overnight at RT. The solvent was evaporated under reduced pressure, the residue was partitioned into water and EtOAc, the separated organic layer was then extracted with water (6x5 cm^3). The combined organic layers was dried over anhydrous Na_2SO_4, and evaporated under reduced pressure to give a pale-yellow solid.



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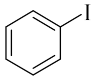
Product obtained as pale-yellow (3.5 g, 79%). mp. 60-62 °C. IR (cm^{-1}): 1608 (C=O) conjugated ketone, 1748 (C=O) ester; ^{1}HNMR (500 MHz, $CDCl_3$) δ (ppm): 1.90 (s, 3H, CH_3), 2.03 (s, 3H, CH_3), 3.77 (s, 3H, OCH_3), 4.05 (s, 2H, CH_2), 5.08 (s, 1H, =CH), 10.88 (br.s, 1H, NH (exchanged with D_2O)); R_f 0.14 (Pet.Ether/EtOAc, 7:3).

Synthesis of an iodobenzene (1) [15]

In 250 cm^3 in a RBF, a mixture of aniline (9.8 cm^3, 107 mmol), conc. hydrochloric acid (27.5 cm^3) and water (27.5 cm^3) was cooled to 5- 6 °C, then a precooled solution of sodium nitrite (8 g, 115.9 mmol) in water (35 cm^3) was added dropwise to keep the internal temperature below 5 °C. A solution of potassium iodide (18 g, 108.43 mmol) in water (20 cm^3) was added and evolve of nitrogen was noticed. The mixture was allowed to stand for one hour in ice bath, and then the reaction mixture was cautiously heated in a boiling water bath until evolution of gas ceases (about 2.5 h). The mixture was allowed to cool, and decant the aqueous layer. The residual aqueous and organic mixture was turned to alkaline by cautious addition of 10 % sodium hydroxide solution (35.5 cm^3) and the alkali converts any phenol present into sodium phenoxide. The crude was dried with anhydrous Na_2SO_4 and purified by distillation (50% yield).

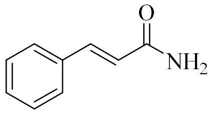


1

A pale-yellow liquid (the compound gradually develops a dark yellow colour upon exposure to light), (11.10 g, 50%, 6 cm^3). IR (cm^{-1}): 3058 (=C-H), 1571and 1471(C=C). R_f 0.8 (Pet.Ether/Acetone, 7:3).

General Procedure of the Heck reaction for synthesis of Cinnamamide (8)

A mixture of iodobenzene 5 (1 to 1.25 equivalents), acrylamide (1 to 1.8 equivalents), Pd $(OAc)_2$ (1-10 mol%), ligand 59 (1 equivalent of Pd $(OAc)_2$) or PPh_3 (2 equivalent of Pd $(OAc)_2$) and Et_3N (1 to 1.5 equivalent) in MeCN was heated at reflux temperature. The completion of reaction was monitored by TLC, after consuming of the limiting substrate the mixture was filtered, concentrated, water was added and the mixture was extracted with EtOAc or $CHCl_3$. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to give a white or red crude solid.

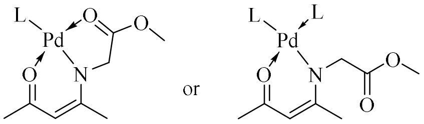


8

Product obtained as a white to red solid. mp. at (147-149) °C [lit. m.p. 148-149 °C].**[16]** IR (cm^{-1}): 3372 and 3168 (asym. and sym. N—H, respectively), 1661 (C=O), 1606 (C=C). R_f 0.2 (Pet.Ether/Acetone, 7:3).

Preparation the catalysis complex (15) of heck reaction [17]

Pd (OAc) $_2$ (0.269 g, 1.2 mmol) was added to a solution of ligand **14** (0.205 g, 1.2 mmol) in Et_3N (0.102 g, 1.2 mmol) EtOH (18 cm^3). The mixture was stirred for (1 h), then heated at reflux for (20 min) and again stir overnight, concentrated under reduced pressure to give a dark green crude solid which was recrystallized from (Pet.Ether/ACN, 1:2)



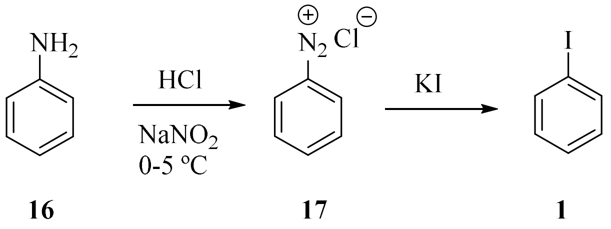
15-A **15-B**

Product was obtained as green crystals (100 mg, 21.4%). mp. at 247 °C (decomposed). IR (cm^{-1}): 1592 (C=O) conjugated ketone, 1740 (C=O) ester; ^{1}HNMR (500 MHz, DMSO-d^6) δ (ppm): 1.77 (s, 3H, CH_3), 1.88 (s, 3H, CH_3), 3.62 (s, 3H, OCH_3), 4.10 (s, 2H, CH_2), 4.95 (s, 1H, =CH); EI-MS (m/z): $[M-L-H]^+$ calcd. for $C_8H_{11}NO_3Pd$, 274.98; found, 275.05; UV absorption appeared as broad peak at 335 nm.

Results and Discussion

Preparation of iodobenzene [15]

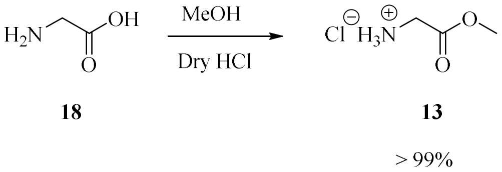
For synthesis of iodobenzene (**1**), aniline (**16**) was used to form the corresponding diazonium salt (**17**), followed by reaction with potassium iodide to afford iodobenzene in moderate yield **(Scheme 4)**.



Scheme 4

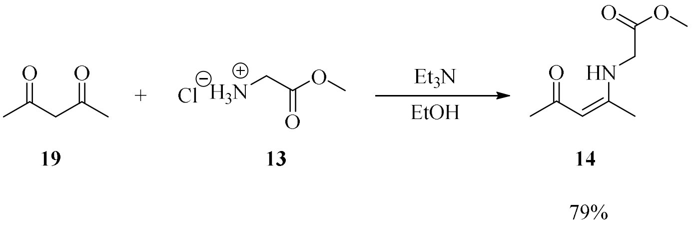
Synthesis of Schiff base methyl (*Z*)-(4-oxopent-2-en-2-yl)glycinate (13) [14]

Firstly, the amino acid glycine **(18)** was esterified by methanol in the presence of acetyl chloride as a source of dry HCl to produce methyl glycinate hydrochloride in quantitative yield **(Scheme 5)**.



Scheme 5

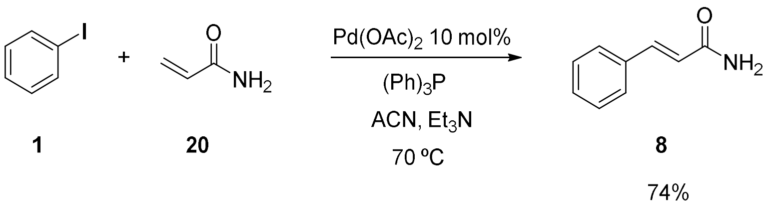
The resultant methyl glycinate **(13)** was reacted with 1,3-dicarbonyl (acetylacetone) **(19)** to yield a multi-dentate ligand, methyl (*Z*)-(4-oxopent-2-en-2-yl)glycinate **(14)** in very good yield **(Scheme 6)**.



Scheme 6

3.3 Use of triphenylphosphine in Heck reaction

According to Park and co-workers [17] who published the synthesis of cinnamamide derivatives as precursor leading the corresponding amines. An initial experiment was carried out between iodobenzene **(1)** and acrylamide **(20)** using $Pd(OAc)_2$ but triphenylphosphine with ratio metal to ligand 1:2 respectively was utilized instead tri-*o*-tolylphosphine as mentioned in their work (Entry **1**, Table 1) **(Scheme 7)**.



Scheme 7

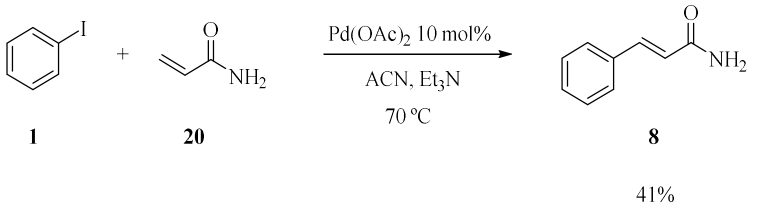
The outcome of this experiment was very good and the amide (**8**) was obtained in 74% yield (Entry **1**, Table 1).

Use of HPLC for yield calculations

Various experiments were performed to reach to the optimized reaction conditions, and due to the lack of the column chromatography requirements such as a silica gel and solvents for mobile phase. Thus, the advantages of reversed phase HPLC was used to calculate the yield% from the crude of cinnamamide in each experiments. The results are summarized in table 1 presented below.

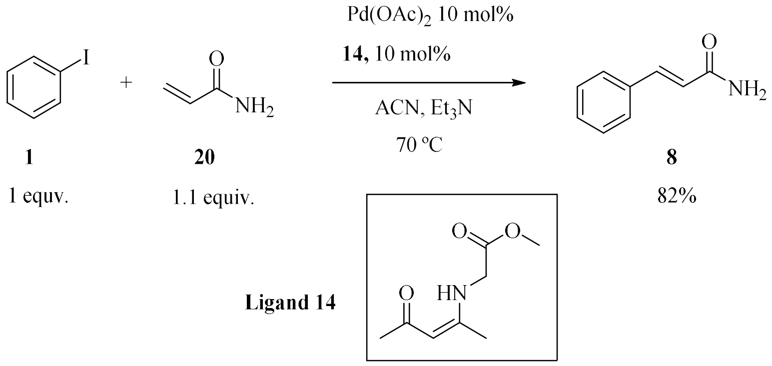
Application of methyl (*Z*)-(4-oxopent-2-en-2-yl)glycinate on Heck coupling reaction to synthesize cinnamamide.

Few published works [18, 19] showed that with particular substrates Heck coupling reaction could be achieved, thus, $Pd(OAc)_2$ catalyzed reaction of iodobenzene **(1)** and acrylamide **(20)** in absence of phosphine ligand was performed, trimethylamine was used as base to accelerate the reductive elimination and the solvent was acetonitrile. The product cinnamamide **(8)** was obtained in (41%) (Entry **2**, Table 1) **(Scheme 8)**.



Scheme 8

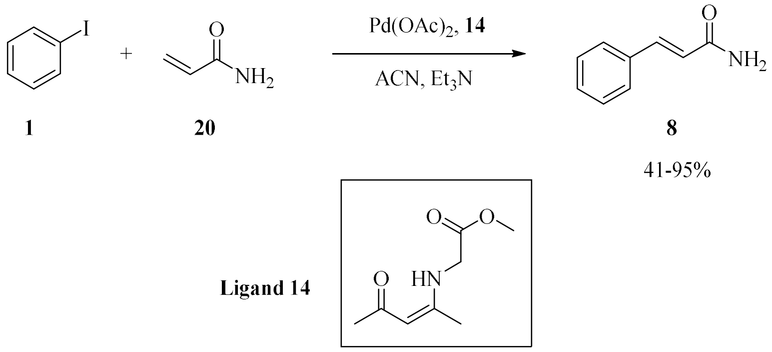
Subsequently, the newly palladium synthesized complex of methyl (*Z*)-(4-oxopent-2-en-2-yl)glycinate **(14)** was examined initially with ratio of 1:1 Pd:Ligand, while the number of equivalents of the acrylamide was 1.1 of iodobenzene. The reaction firstly started with preparation of the complex in-situ until change in the colour of palladium solution was noticed, then the mixture solution was followed by iodobenzene and acrylamide (Entry **3**, Table 1) **(Scheme 9)**.



Scheme 9

After the work-up, the crude mixture was separated by short flash column into two fractions both of them showed almost the same IR spectrums, they are fully consistent with cinnamamide IR spectrum, and the two fractions were suggested to be geometrical isomers *Z*- and *E*-cinnamamide. This experiment showed the in-situ synthesis of the catalyst seems to have enhanced the rate of Heck coupling reaction by comparing 82% (in presence of ligand **14**) with 41% (in absence of ligand **14**).

Optimization the Heck reaction conditions



Scheme 10

Further modifications were carried out on the above reaction **(Scheme 10)** to reach a higher yield. The completion of Heck reaction in each experiment was monitored by TLC, an excess of iodobenzene was noticed, which mean the conversion% was not 100%. Accordingly, iodobenzene was chosen to be the limited reagent, while the excess material became the acrylamide, this change was expected to simplify the purification of crude having the fact that acrylamide is water-soluble (Entry **3-8**).

Table 1: The outcome of various Heck reaction conditions for the synthesis of cinnamamide from acrylamide.

No	Heck Reaction Conditions						HPLC yield%	TON	TOF min^{-1}
	Ph-I	**Acrylamide**	**Temp. (°C)**	**Time (hrs)**	**Ligand**	**Pd-compl. mole%**			
1	1.1	1	70	2	PPh_3	10	74	819	410
2	1.1	1	70	1.5	Ligand free	10	41	448	299
3	1	1.1	70	1.5	**(14)**	10	82	817	545
4	1	1.3	70	4	**(14)**	10	72	723	181
5	1	1.5	70	2	**(14)**	10	89	887	443
6	1	1.8	80	2	**(14)**	10	95	1269	634
7	1	1.5	80	5	**(14)**	5	93	1853	371
8	1	1.5	80	5	**(14)**	1	71	7067	1413

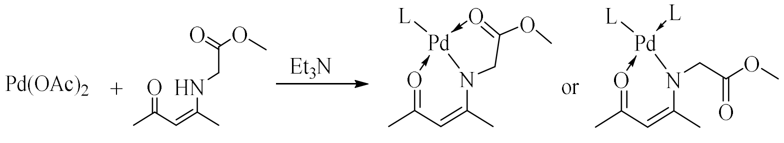
L= Methyl (*Z*)-(4-oxopent-2-en-2-yl)glycinate, **14**

Increasing the number of equivalents of acrylamide from 1.1 (Entry **3**) to 1.8 equivalents (Entry **6**) of iodobenzene enhanced the yield from 82% to 95% while the turnover number (TON) was increased from 817 to 7067.

The best combination results the yield% (93%) and TON (1853) were obtained when loading of the catalyst diminished to 5 mol% (Entry **7**). While decreasing of the catalyst further to 1 mol% lead to increasing TON value to be 7067, *i.e.* about 16 times faster than the free ligand reaction and nearly 9 times more efficient than use of the common ligand PPh_3. However, the yield% lowered to 71% (Entry **8**). In addition, the turnover frequency (TOF) was calculated, the highest TOF value was reached when the catalyst loading diminished to 1 mol% (Entry **8**) but it was accompanied with decreasing of the yield% of the product 71%. Thus, it is compromising between the catalytic efficiency and yield%, which suggest the work need more tuning in future work to reach the optimum results.

Synthesis of palladium complex (15)

To ensure the in-situ formation the complex and investigate the complex properties, synthesis of the complex **(15)** was accomplished. The spectral characterization by UV and IR spectroscopy gave some evidences that support the formation of the complex. UV spectrum showed metal-ligand charge transfer (MLCT) absorption as a broad peak at 335 nm. In addition, IR spectrum of the recrystallized complex was easily distinguished from IR spectrum of the ligand. Also, decreasing the frequencies of functional groups such as the ketonic and esteric C=O, C=C-N of the enamine group, that could be involved in the coordination process. Additionally, comparing the ^{1}HNMR spectrum of the complex with the spectrum of the ligand **14** showed the absence of the acidic proton at 10.88 accompanied with decreasing the chemical shift of the most peaks. All of the above observations support formation of the complex **(15) (Scheme 11)**. In IR spectrum, the decreasing of the wave number of ester carbonyl and the shift of OMe absorption in ^{1}HNMR suggest that the ligand **(14)** may combined with palladium atom as tridentate ligand.



14 **15-A** **15-B**

Scheme 11

Conclusion

Methyl (*Z*)-(4-oxopent-2-en-2-yl)glycinate have been synthesized as a multi-dentate ligand by reaction of methyl glycinate hydrochloride and commercially available acetylacetone. The formed ligand was complexed with $Pd(OAc)_2$ and it was investigated as a new catalyst of Heck coupling reaction of aryl iodide with acrylamide, cinnamamide were obtained in good to excellent yields. The highest turnover number (TON) and turnover frequency (TOF) of the catalytic system of this reaction were reached to 7067 and 1413, respectively. Additionally, formation of the palladium complex was confirmed when it was isolated and identified by spectroscopic techniques.

References

[1] Hagen J. *Industrial catalysis : a practical approach.* Weinheim: WILEY-VCH; 2008.

[2] Jagtap S. Heck Reaction—State of the Art. *Catalysts*. 2017;7:267.

[3] Solomons TWG, Fryhle CB, Snyder SA. *Organic chemistry.* Hoboken: John Wiley & Sons, Inc. 2017.

[4] Kürti L, Czakó B. *Strategic applications of named reactions in organic synthesis* London: Elsevier Academic Press 2014.

[5] Dieck HA, Heck RF. Organophosphinepalladium complexes as catalysts for vinylic hydrogen substitution reactions. *Journal of the American Chemical Society*. 1974;96:1133-6.

[6] Gunia-Krzyżak A, Pańczyk K, Waszkielewicz AM, Marona H. Cinnamamide Derivatives for central and peripheral nervous system disorders—A review of structure–activity relationships. *ChemMedChem*. 2015;10:1302-25.

[7] Natella F, Nardini M, Di Felice M, Scaccini C. Benzoic and cinnamic acid derivatives as antioxidants: Structure− activity relation. *Journal of agricultural and food chemistry*. 1999;47:1453-9.

[8] Leslie BJ, Holaday CR, Nguyen T, Hergenrother PJ. Phenylcinnamides as novel antimitotic agents. *journal of Medicinal chemistry*. 2010;53:3964-72.

[9] Cutillo F, D'Abrosca B, DellaGreca M, Di Marino C, Golino A, Previtera L, et al. Cinnamic acid amides from Chenopodium album: effects on seeds germination and plant growth. *Phytochemistry*. 2003;64:1381-7.

[10] Castral TC, Matos AP, Monteiro JL, Araujo FM, Bondancia TM, Batista-Pereira LG, et al. Synthesis of a combinatorial library of amides and its evaluation against

the fall armyworm, Spodoptera frugiperda. *Journal of agricultural and food chemistry*. 2011;59:4822-7.

[11] Guan L-P, Sui X, Deng X-Q, Zhao D-H, Qu Y-L, Quan Z-S. N-palmitoylethanolamide derivatives: synthesis and studies on anticonvulsant and antidepressant activities. *Medicinal Chemistry Research*. 2011;20:601-6.

[12] Zhou X-Y, Chen X, Wang L-G. Recycled Pd/C-Catalyzed Heck Reaction of 2-Iodoanilines under Ligand-Free Conditions. *Synthesis*. 2017;49:5364-70.

[13] Dondoni A, Perrone D. Synthesis of 1, 1-Dimethylethyl (S)-4-Formyl-2, 2-Dimethyl-3-Oxazolidinecarboxylate by Oxidation of the Alcohol: 3-Oxazolidinecarboxylic acid, 4-Formyl-2, 2-Dimethyl-, 1, 1-Dimethylethyl Ester. *Organic Syntheses*. 2003;77:64.

[14] Hombrecher HK, Horter G. Synthesis of Pyrroles via Ethyl N-(3-Oxo-1-alkenyl) glycinates. *Synthesis*. 1990;1990:389-91.

[15] Furniss BS, Vogel AI. *Vogel's textbook of practical organic chemistry*. Harlow: Pearson/Prentice Hall; 2009.

[16] Zhang L, Wang S, Zhou S, Yang G, Sheng E. Cannizzaro-Type Disproportionation of Aromatic Aldehydes to Amides and Alcohols by Using Either a Stoichiometric Amount or a Catalytic Amount of Lanthanide Compounds. *The Journal of Organic Chemistry*. 2006;71:3149-53.

[17] Park N-S, Baek GH, Cho SJ, Jung YS, Seong C-M, Lee C-W. Synthesis of 3-arylpropylamine derivatives from aryl halides using Heck reaction. *Bulletin of the Korean Chemical Society*. 1999;20:232-6.

[18] Chen X, Zhou X-Y, Wang L-G. Palladium catalyzed Heck reaction of 2-iodoanilines under ligand-free conditions in air. *Synthetic Communications*. 2017;47:2096-102.

[19] Yao Q, Kinney EP, Yang Z. Ligand-free Heck reaction: Pd (OAc) 2 as an active catalyst revisited. *The Journal of Organic Chemistry*. 2003;68:7528-31.