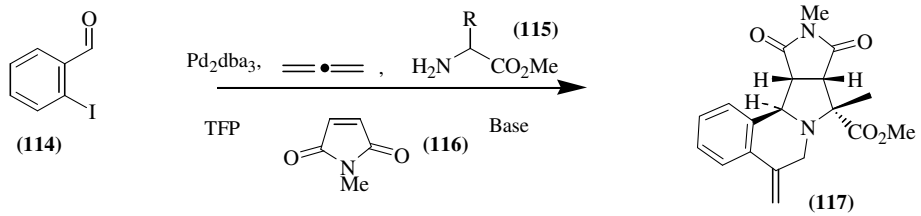
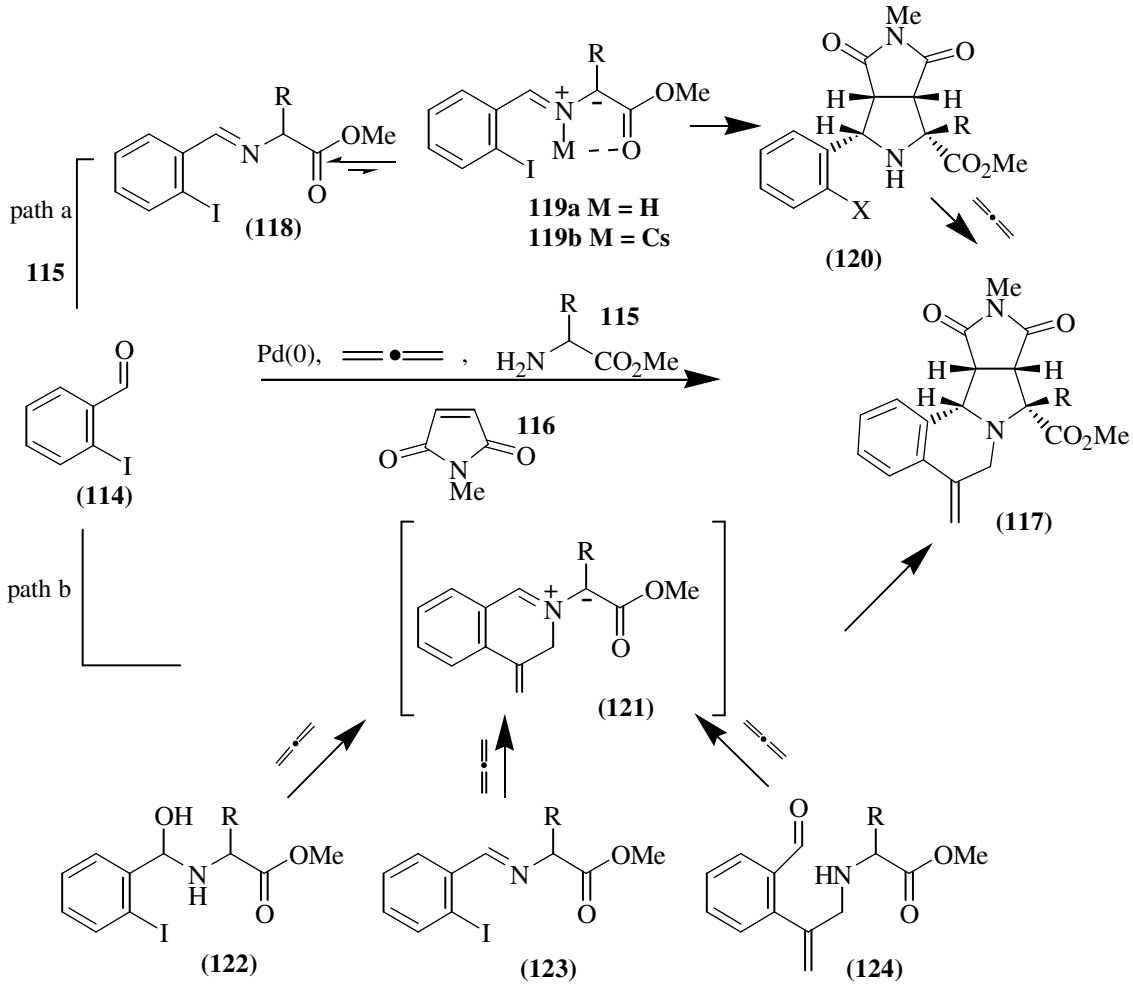
RESULTS AND DISCUSSION

The main purpose of this research was to study the palladium-catalyzed four-component cascade reaction of 2-iodobenzyl aldehyde (114), amino acid methyl ester (115), allene and NNM (116) in the presence of $Pd_2(dba)_3$ (2.5 mol%) and tris(2-furyl)phosphane (TFP) (10 mol%)) (Scheme 10).



Scheme 10

Two plausible mechanisms might be involved in the reaction (Scheme 11). 2-iodobenzyl aldehyde (114) was reacted with allene, amino acid methyl ester (115), and *N*-methyl maleimide (96) in the presence of Pd(0) to afford (117) via path a or path b. Path a involves formation of imine (118), which undergoes 1,3-dipolar cycloaddition via the azomethine ylide (119a) or (119b) (endo transition state) to give (120). Successive palladium catalyzed allene/nucleophile incorporations then afford (117). In path b, palladium catalyzed allenylation / nucleophile incorporation generated azomethine ylide (121) which undergoes a 1,3-dipolar cycloaddition to afford 97. Azomethine ylide (121) could arise via the precursors (122), (123) or (124).



Scheme 11

The four-component cascade reaction of 2-iodobenzaldehyde (114) (1 mmol) was investigated by reacting with allene (1 bar), phenyl glycine methyl ester hydrochloride (125) (1.2 mmol), *N*-methyl maleimide (116) (1 mmol), Pd_2dba_3 (2.5 mol%), TFP(10 mol%) and K_2CO_3 (4 mol eq) in toluene 10 ml at 100°C for 48 h. The product (126) was obtained in low yield (15%) (Table 2, Entry 1).

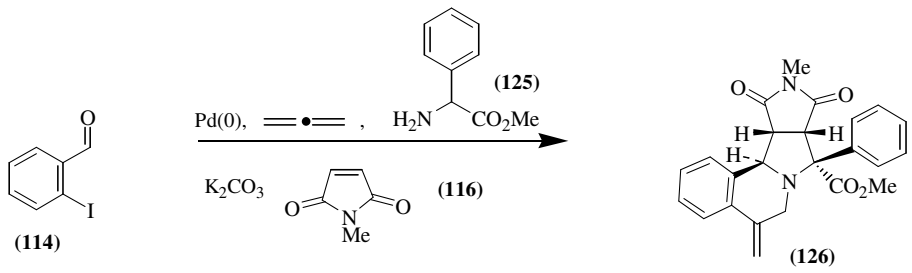
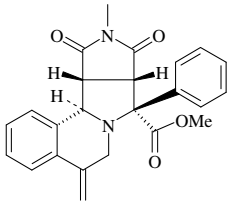
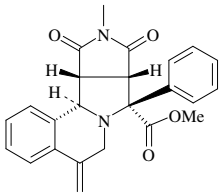
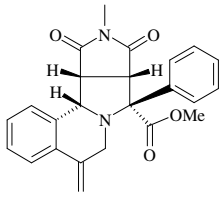


Table 2 Reaction optimization of phenyl glycine methyl ester hydrochloride (125)

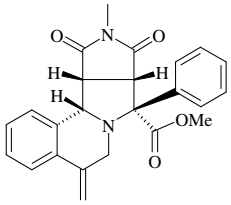
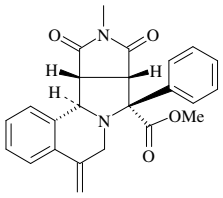
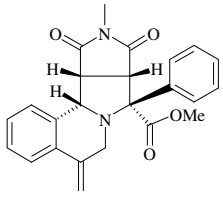
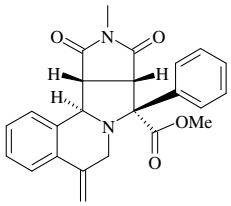
Entry	Base (4 mol eq.)	Time (h)	Results
1	K_2CO_3	48	 **126** (15%)
2	DBU	48	Complex mixture
3	Cs_2CO_3	48	 **126**(31%)  **127**(34%)

To increase the yield of (126), the reaction was optimized by changing base. In the case of organic base DBU, only a complex mixture (Table 2, entry 2) was observed. Explanation of this unsuccessful result (Table 2, entry 2) is still not clear since DBU is employed in normal 1,3-dipole cycloaadition reactions to afford cycloadducts in a good yield (Grigg *et al*., 1995). DBU might interfere in palladium-catalyzed allenylation step. An inorganic base Cs_2CO_3, was also employed in cascade reaction to afford a mixture of diastereomer (126) (31%) and (127) (34%) (Table 2, entry 3). This result was indicated that Cs_2CO_3 is a more active base than K_2CO_3 and lead to the satisfactory yield but gives a mixture of diastereomers (126) and (127). The configuration of (126) and (127) were established by n.O.e. studies.

The reaction time of cascade reaction was also optimized (Table 3). Interestingly, decreasing the reaction time to 12 h led to only kinetic product (127) in

59% yield (Table 3, entry 1) whilst increasing the reaction time to 72 h afforded only thermodynamic product (126) in 31% (Table 3, entry 3). This suggested that (126) might arise via the epimerization of (127) or alternatively (127) underwent a retro 1,3-dipolar cycloaddition reaction to generate syn azomethine ylide which then underwent stereo mutation to generate anti azomethine ylide followed by 1,3-dipolar cycloaddition reaction.

Table 3 Reaction time optimization of phenyl glycine methyl ester hydrochloride (125)

Entry	Base (4 mol eq.)	Time (h)	Results
1	Cs_2CO_3	12	 126(59%)
2	Cs_2CO_3	24	 126(13%)  127(45%)
3	Cs_2CO_3	72	 126(31%)

We also used a range of amino acid methyl esters in the four-component cascade reaction. Amino acid methyl esters were employed in cascade reaction by using 2-iodo-benzyldehyde (114), *N*-methyl maleimide (116) (1 mmol), Pd_2dba_3 (2.5 mol%), TFP(10 mol%) and Cs_2CO_3 (4 mol eq) in toluene 10 ml at 100ºC for 24 h (Table 4).

Table 4 Four-component cascade reaction of amino acid methyl esters

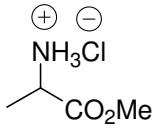
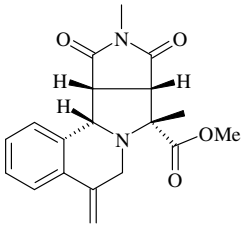
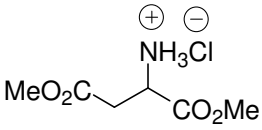
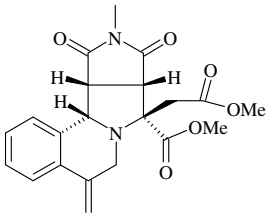
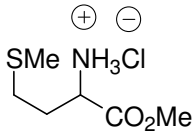
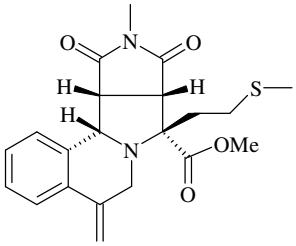
Entry	Amino acid methyl esters (1.2 mol eq.)	Results
1	 Alanine methyl ester (129)	 **139**(67%)
2	 Aspartic methyl ester (130)	 **140**(57%)
3	 Methionine methyl ester (131)	 **141**(56 %)

Table 4 (Cont'd)

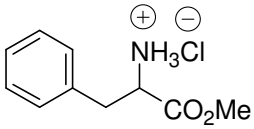
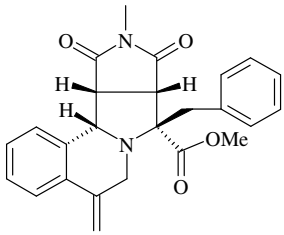
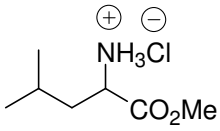
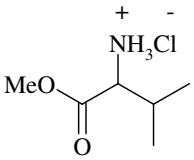
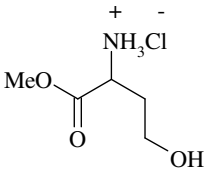
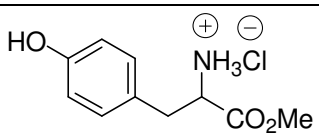
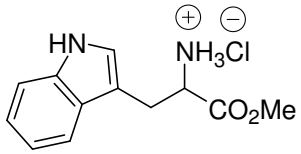
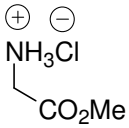
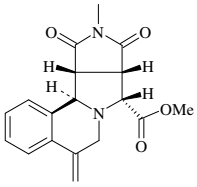
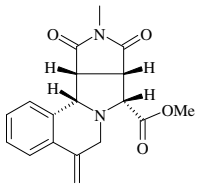
Entry	Amino acid methyl esters (1.2 mol eq.)	Results
4	 Phenyl alanine methyl ester (132)	 **142**(55%)
5	 Leucine methyl ester(133)	Complex mixture
6	 Valine methyl ester (134)	Complex mixture
7	 Serine methyl ester (135)	Complex mixture
8	 Tyrosine methyl ester (136)	Complex mixture

Table 4 (Cont'd)

Entry	Amino acid methyl esters (1.2 mol eq.)	Results
9	 Tryptophan methyl ester (137)	Complex mixture
10	 Glycine methyl ester (138)	 (143)  (144) 1 :1 inseparable mixture (53%)

In the case of leucine methyl ester (133), valine methyl ester (134), serine methyl ester (135), tyrosine methyl ester (136) and tryptophan methyl ester (137) (Table 4, entry 5-9), the four-component cascade reactions did not provide the expected products but gave only complex mixture. The possible explanations of these unsuccessful results (Table 4, entry 5-9) are steric hindrance of amino methyl esters (Table 4, entry 5-6) or that the amino methyl esters are unstable under the reaction condition (Table 4, entry 7-9) or the reaction times are too long and cycloadducts decompose.

However, alanine methyl ester (129), aspartic acid methyl ester (130), methionine methyl ester (131) and phenylalanine methyl ester (132) were

successfully employed in the cascade reaction (Table 4, entry 1-4) to give (139)-(142) in 54-67% yield.

Interestingly, glycine methyl ester (138) was employed under the above cascade under essentially same conditions to afford a 1:1 mixture of inseparable diassteromer (143) and (144) in 53% yield. The ratio of diastereomers (143) and (144) was determined by the integration of ^{1}H NMR spectra (Table 1, entry 6). It was found that decreasing the reaction time of the cascade reaction to 12 h led to only kinetic product (144) in 68% yield.

The four-component cascade reaction of a range of amino acid methyl esters led to the kinetic products via 1,3-dipolar cycloaddition of azomethine ylide (endo transition state) with NMM (116). Therefore, the mechanism of four-component cascade reaction is more likely to proceed via path a than path b.