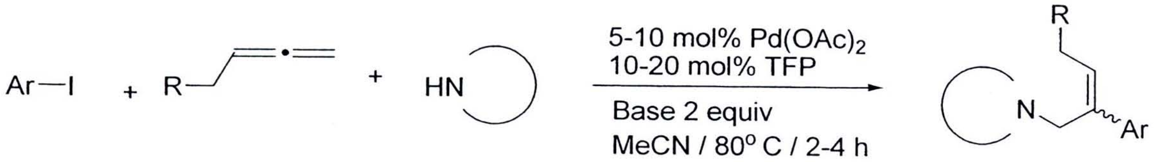
CHAPTER 3

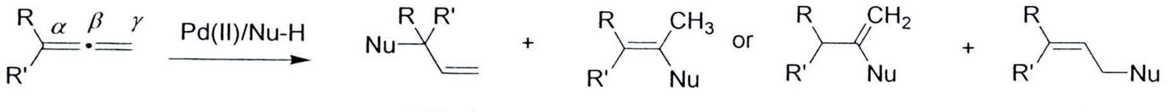
RESULTS AND DISCUSSION

We have investigated three-component cascade reaction involving an aryl iodide, quinazolinone allene and secondary amines.



It was found that incorporating the quinazolinone allene into the three-component cascade process produced a trisubstitued olefin regio- and stereo-selectively.

The addition of nucleophile to substituted allenes can present three possible regioisomers depending on the terminal carbon of the allenes. The α- and γ-adducts are the usual products whilst the β-adducts occur much less frequently.

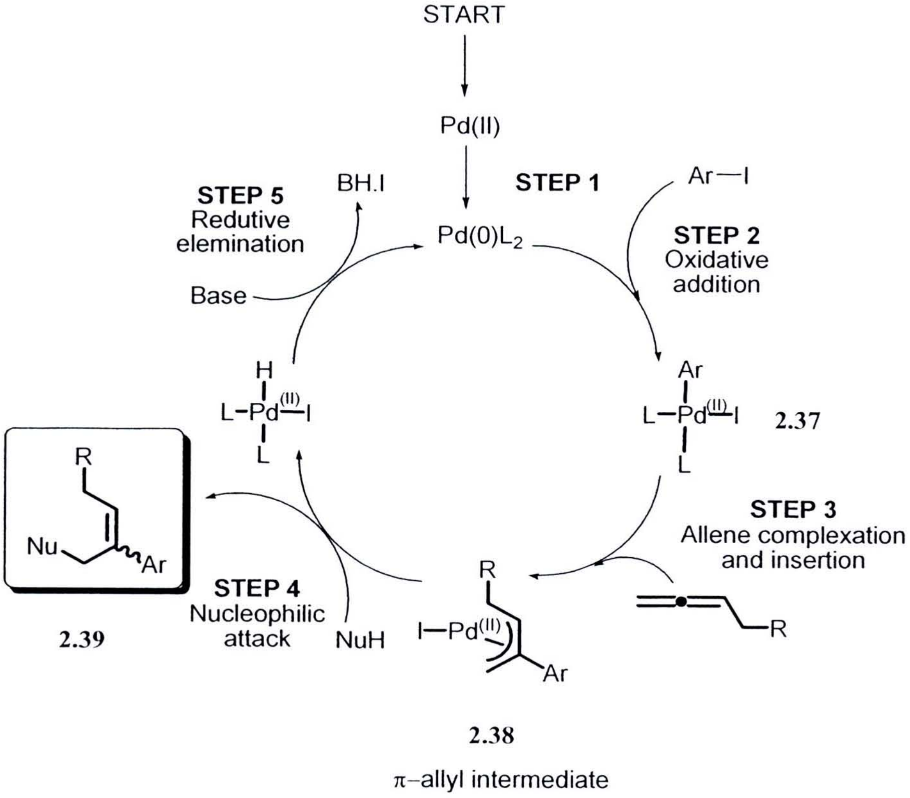


α-adduct β-adduct γ--adduct

2.33 **2.34** **2.35** **2.36**

Mechanism

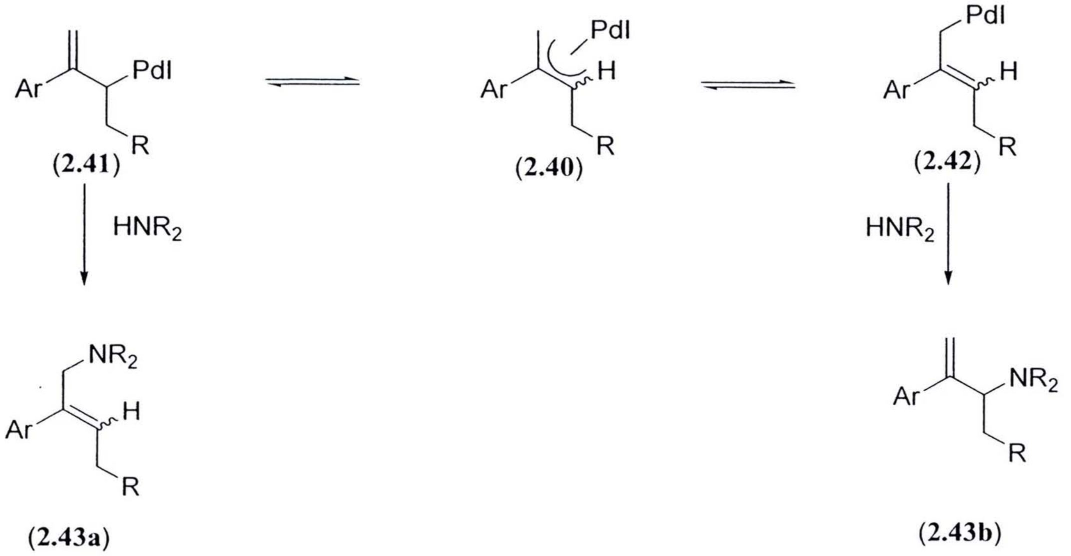
The mechanism of the three-component palladium catalysed allenylation of aryl iodides and nucleophile is believed to proceed via the catalytic cycle shown in Scheme 6. Step 1, the active catalyst was proposed as zerovalent palladium generated from palladium (II) acetate by ligand exchange with tris(2-furyl)phosphine (TFP). Step 2, is oxidative addition of Pd(0) to the aryl iodide gave arylpalladium (II) iodide intermediate (**2.37**). Step 3, an allene inserted to arylpalladium (II) iodide intermediate and generated the allyl species **2.38**. Step 4, nucleophilic attack at the least sterically hindered carbon of π-allyl species generated the product (**2.39**) and a palladium (II) hydride species. The last step regenerated the Pd(0) via reductive elimination of Pd(II) by base (Scheme 1).



Shceme 1 Mechanism of the three-component palladium catalyzed reaction

Regiochemistry

Two regioisomer, the α- and γ-adduct are possible in this reaction when a monosubstituted allene is employed. In Scheme 2 the palladium complex **2.40** was proposed to be in equilibrium with its two form **2.41** and **2.42**. These two form-complexes can undergo nucleophile attack to yield products (Scheme 2).

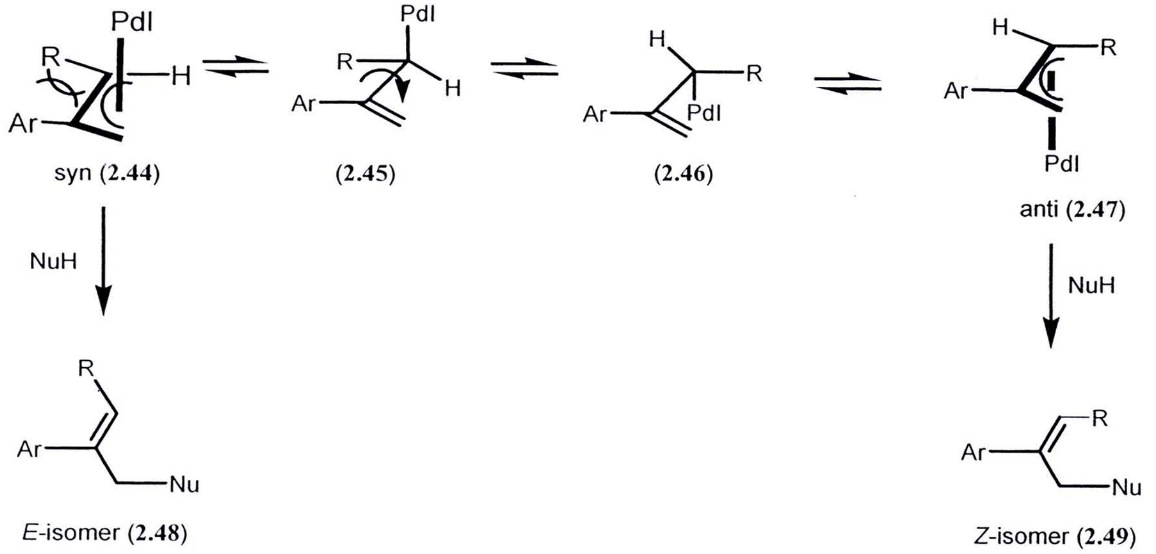


Scheme 2 Proposed regioselective formation of products

We would expect the rate of nucleophilic attack to be sensitive to the steric effects and hence the production of **2.43b** would be affected because of the large bulky R group. The preferred product would therefore be **2.43a**, since the path of the incoming nucleophile is relatively less hindered and resulted in the formation of more thermodynamically stable double bond. Only one regioisomer formed regardless of the allene used.

Stereochemistry

Monosubstituted allenes can furnish to both *syn* and *anti* π-allyl complexes thus nucleophilic attack on these complexes generating both *E*- and *Z*-isomers are possible. The *syn* and *anti* π-allyl complexes can equilibrate via the corresponding σ-complexes **2.45** and **2.46** (Scheme 3).



Scheme 3 Proposed routes to *Z*- and *E*-isomers

Nucleophilic attack by the secondary amine on the *anti*-π-allyl palladium complex **(2.47)** generated the *Z*-isomer **(2.49)**, whereas attack on the less hindered site of the *syn*-π-allyl palladium complex gave rise to the *E*-isomer **(2.48)**. The equilibrium of the anti-π-allyl palladium complex **(2.47)** with the *syn*-π-allyl palladium complex **(2.44)** depends on the relative rates of this process and the rate of nucleophilic attack. The formation of the *E*-isomer **(2.48)** is disfavoured owing to the strong steric interaction in the *syn*-π-allyl palladium complex **(2.44)** between the aryl and the allene substituent R group.

Palladium Catalyzed Three-Component Cascade Reactions

1,3,4-Triazole-Subtituted Tropane as Nucleophile

Palladium-catalyzed three-component cascade reaction of an aryl iodide, quinazolinone allene, and 1,3,4-triazole-subtituted tropane produced a trisubstituted olefin in good yield (Table 1).

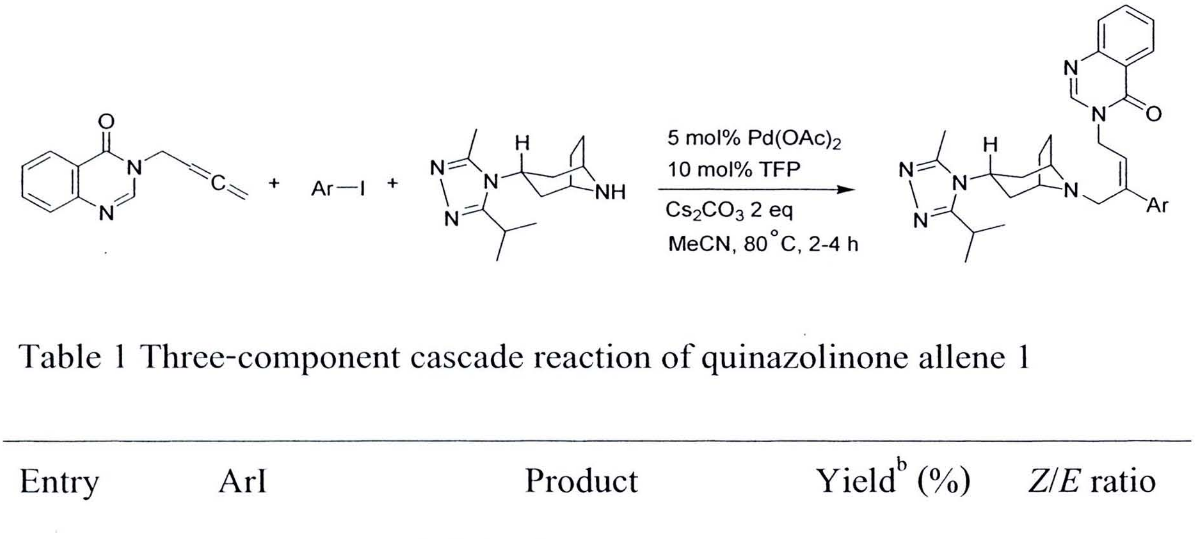


Table 1 Three-component cascade reaction of quinazolinone allene 1

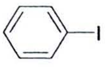
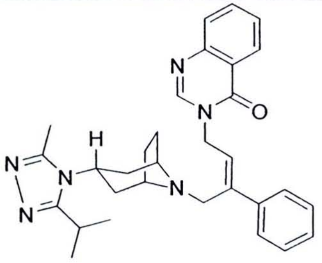
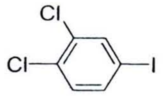
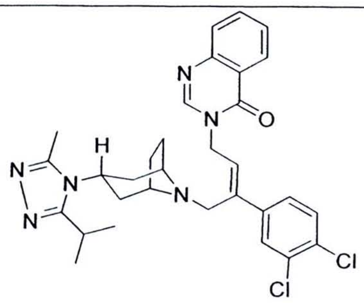
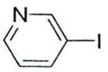
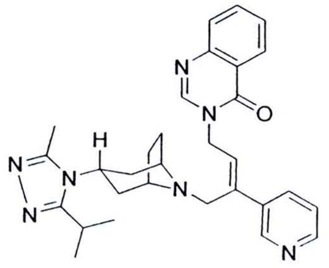
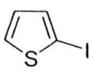
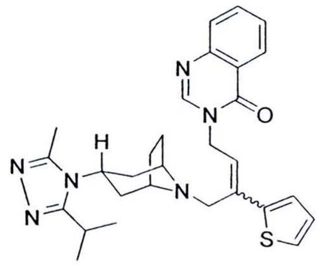
Entry	ArI	Product	Yield[b] (%)	*Z*/*E* ratio
1[a]		 **2.24**	96	100:0

Table 1 (continued)

Entry	ArI	Product	Yield[b] (%)	*Z*/*E* ratio
2[a]		 **2.25**	92	100:0
3[a]		 **2.26**	69	100:0
4[a]		 **2.27**	80	1:2.6

[a] Reaction carried out in MeCN at 80 °C for 2-3 h and employed ArI (0.5 mmol), amine (0.6 mmol), allene (0.5 mmol), $Pd(OAc)_2$ (5 mol%), TFP (10 mol%) and Cs_2CO_3 (1.0 mmol).
[b] Isolated yield.

This reaction gave the Z-isomer (Table 1), except for entry 4, which afforded the mixture of *Z*:*E*-isomer. It may be explained by Scheme 3 that shows the *anti*-π-allyl complex **(2.47)** favoured more than the syn-π-allyl complex **(2.44)**, due to steric hindrance between the aryl and quinoline allene. So the equilibrium will lie towards the anti-π-allyl complex and gave *Z*-isomer. 2-Iodothiophene afforded the mixture *Z*:*E* ratio may be due to less steric effect of quinazolinone allene and it small size.

Piperazine Amine as Nucleophile

Palladium-catalyzed three-component cascade reaction of an 5-iodoindole, quinazolinone allene, and piperazine produced the mixture of *Z*:*E*-isomer in 62-79% yield (Table 2).

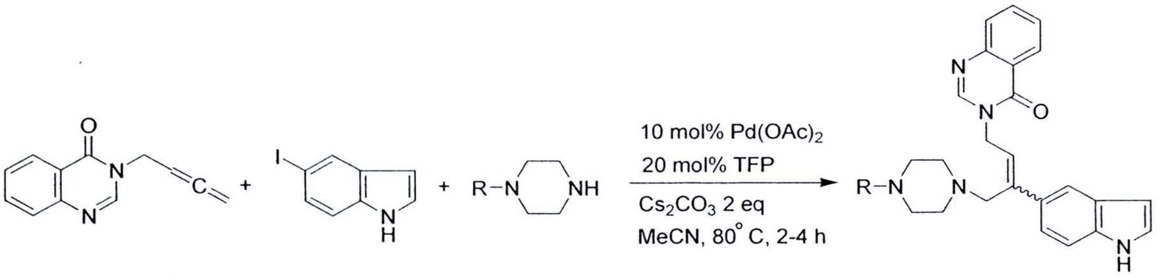


Table 2 Three-component cascade reaction of quinazolinone allene 2

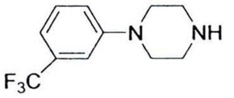
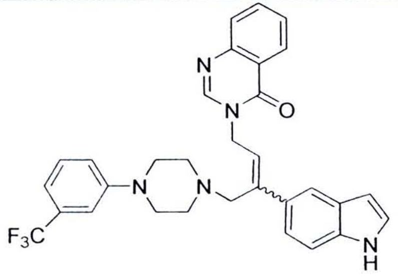
Entry	Amine	Product	Yield[b] (%)	*Z*/*E* ratio
1[a]		 **2.28**	66	5.4:1

Table 2 (continued)

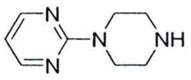
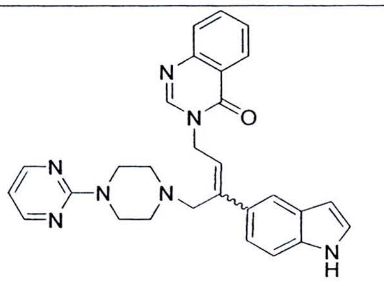
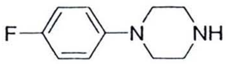
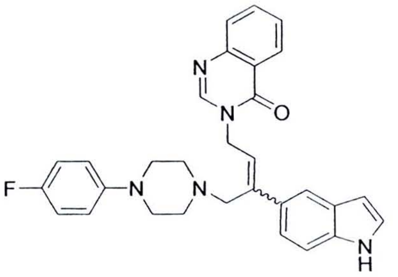
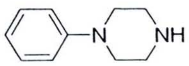
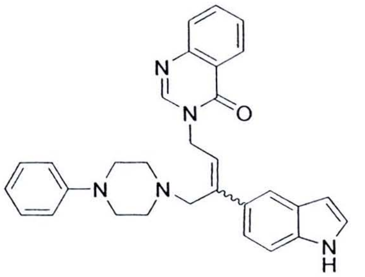
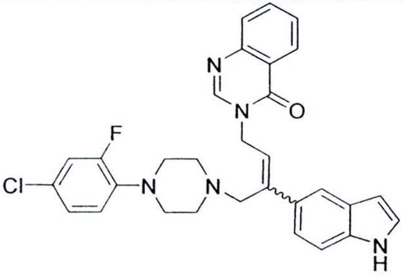
Entry	Amine	Product	Yield[b] (%)	*Z*/*E* ratio
2[a]		 **2.29**	79	6.8:1
3[a]		 **2.30**	67	5:1
4[a]		 **2.31**	62	7:1

Table 2 (continued)

Entry	Amine	Product	Yield[b] (%)	Z/E ratio
5[a]		 **2.32**	62	6.2:1

[a] Reaction carried out in MeCN at 80 °C for 2-4 h and employed ArI (0.5 mmol), amine (0.6 mmol), allene (0.5 mmol), $Pd(OAc)_2$ (10 mol%), TFP (20 mol%) and Cs_2CO_3 (1.0 mmol).

[b] Isolated yield.