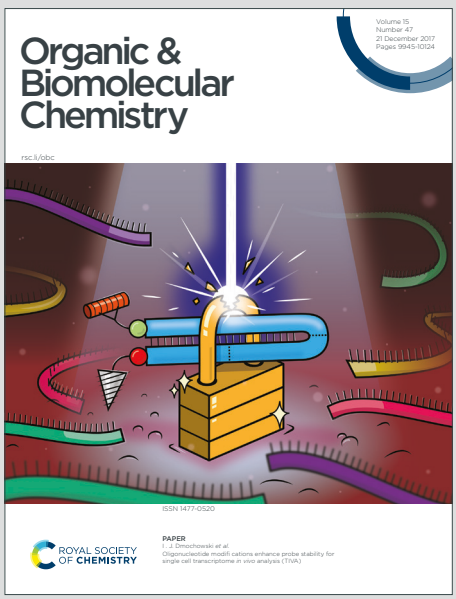
Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: S. R. Meesa, P. K. Naikawadi, K. Gugulothu and S. K. Kota, *Org. Biomol. Chem.*, 2020, DOI: 10.1039/D0OB00318B.



ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/D0OB00318B

COMMUNICATION

Catalyst and solvent switched divergent C–H functionalization: oxidative annulation of *N*-aryl substituted quinazolin-4-amine with alkynes

Received 00th January 20xx,
Accepted 00th January 20xx

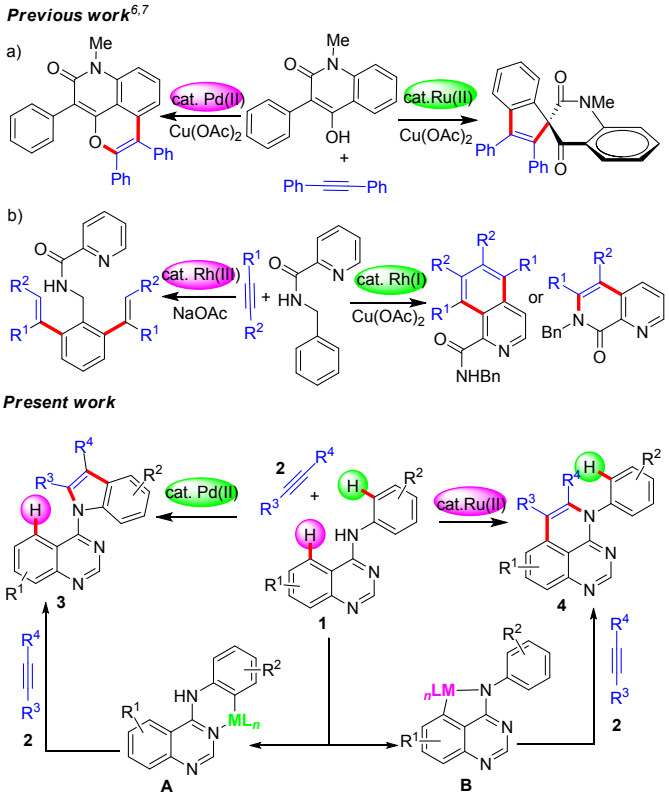
DOI: 10.1039/x0xx00000x

Siddi Ramulu Meesa, Praveen Kumar Naikawadi, Kishan Gugulothu, K. Shiva Kumar*

The development of site-selective C–H functionalizations/annulations is one of the most challenging practices in synthetic organic chemistry particularly for substrates bearing several similarly reactive C–H bonds. Herein, we describe catalyst and solvent controlled *ortho*/*peri* site-selective oxidative annulation of C–H bonds of *N*-aryl substituted quinazolin-4-amines with internal alkynes. The *ortho* C–H selective annulation was observed using Pd-catalyst in DMF to give indole-quinazoline derivatives, while, Ru-catalyst in PEG-400 favoured the *peri* C–H bond annulation exclusively to furnish pyrido-quinazoline derivatives.

Regioselective C–H bond functionalizations/annulations is one of the most challenging practices in synthetic organic chemistry particularly for substrates bearing several similarly reactive C–H bonds.[1] Consequently, this has become an important goal in the field of contemporary organic synthesis.[2] Over the past few years, the transition metal-catalyzed C-H activation/functionalization has become a rapidly evolving research field towards the synthesis of bioactive complex polycyclic molecules.[3] However, despite the tremendous progress that has been made, site selectivity remains challenging and the reports describing this phenomena are very limited. Generally, the use of substrate,[4] ligands[5] and catalyst control[6-8] has been explored for the site selective C–H bond functionalizations/annulations.[9] However, the development of strategies for functionalization of distinctive and positional C–H sites on *N*-aryl Substituted quinazolin-4-amine has not been explored till date. Additionally indole/pyridoquinazoline derivatives, have emerged as important building blocks in contemporary synthesis and these frameworks being an integral part of many bioactive molecules is considered important structures in drug discovery.[10]

Lam *et al.* reported the synthesis of spiroindenes/benzopyrans from unsymmetrical 2-aryl cyclic 1,3-dicarbonyl compounds with alkynes/alkenes *via* catalyst and solvent controlled divergent C–H functionalization (Scheme 1a)[6]. Carretero *et al.* delivered a Rh^{III}/Rh^{I}-controlled divergent functionalization of aryl and heteroaryl C–H bonds of picolinamide substrates that produced selectively, isoquinoline-1-carboxamides or *ortho*-olefinated benzylamines (or phenethylamines) (Scheme 1b).[7] As a part of our ongoing studies on the development of new protocols for the C-H activation/functionalizations[11] and construction of functionalized heteroaromatics,[12] we investigated a Ru/Pd catalyzed highly efficient and



Scheme 1 Catalyst/solvent controlled annulations/functionalizations.

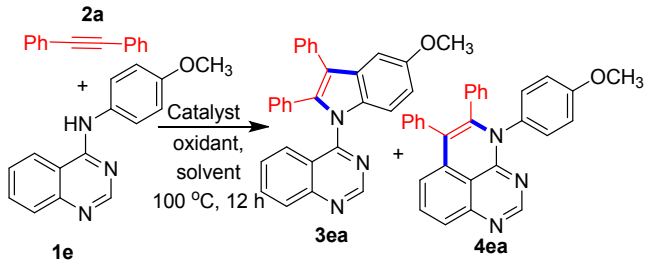
[a] *Department of Chemistry, Osmania University, Hyderabad-500 007, India*
E-mail: shivakumarkota@yahoo.co.in; shivakumarkota@osmania.ac.in.
† Footnotes relating to the title and/or authors should appear here.
Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/D0OB00318B

regioselective functionalization (oxidative annulation) of different C–H bonds of *N*-aryl substituted quinazolin-4-amine with alkynes (Scheme 1c). The selective cleavage of *peri* C–H and *N*-phenyl *ortho* C–H bond of the *N*-phenylquinazolin-4-amine substrates was observed by simple tuning of catalyst and solvent systems, which could provide the selective and straightforward access to indole-quinazolines or pyridoquinazolines.

Our initial investigation focused on the oxidative annulation of the *N*-(4-methoxyphenyl)quinazolin-4-amine (**1e**) with diphenylacetylene (**2a**) in the presence of $Pd(OAc)_2$ (10 mol %) and $Cu(OAc)_2$ (0.3 equiv) at 100 °C in DMF for 12 h under open air furnished the *ortho* C–H bond annulated product of **1e**, i.e., **3ea** as sole product in 45% yield (Table 1, entry 1). When the reaction was carried out with increased quantity of $Cu(OAc)_2$ (0.50 equiv.), no improvement in yield of **3ea** was observed (Table 1, entry 2). With our desire to increase the yield of **3ea**, we used TBAB as an additive for this transformation. To our delight, the product yield was improved to 68% (Table 1, entry 3). The use of oxygen filled in a balloon did not show any significant effect on the yield of **3ea** (Table 1, entry 4). Other oxidants such as $Cu(OAc)_2.H_2O$, Ag_2CO_3 and $AgNO_3$ were screened (Table S1, entries 1-3, Electronic Supporting Information, ESI) when $Cu(OAc)_2$ was proved to be the best (Table 1, entry 3 *vs* Table S1, entries 1-3, ESI). Solvent effects were also examined and the reaction did not proceed well in solvents such as 1,4-dioxane, toluene, DCE, PEG-400 and H_2O (Table S1, entries 4–8, ESI). By lowering or increasing the reaction temperature afforded lower yields of product (Table S1, entries 9-10, ESI). The yield of **3ea** dropped to 52% when the catalyst loading was decreased from 10 mol % to 5 mol% (Table S1, entry 11, ESI). Replacement of the $Pd(OAc)_2$ with $PdCl_2$ resulted in lowering the product yield (Table S1, entry 12, ESI).

Table 1 Optimization of reaction conditions[a]



Entry	Catalyst (mol%)	Oxidant	Solvent	yield[b] (%)	
				3ea	4ea
1	$Pd(OAc)_2$ (10)	$Cu(OAc)_2$	DMF	45	0
2[c]	$Pd(OAc)_2$(10)	$Cu(OAc)_2$	DMF	45	0
3[d]	$Pd(OAc)_2$(10)	$Cu(OAc)_2$	DMF	68	0
4[d]	$Pd(OAc)_2$(10)	$Cu(OAc)_2/O_2$	DMF	65	0
5[d]	$[RuCl_2(p$-cymene$)]_2$(5)	$Cu(OAc)_2$	DMF	28	15
6	$[RuCl_2(p$-cymene$)]_2$(5)	$Cu(OAc)_2$	DMF	35	30
7	$[RuCl_2(p$-cymene$)]_2$(5)	$Cu(OAc)_2$	PEG-400	0	62
8	$[RuCl_2(p$-cymene$)]_2$(5)	$Cu(OAc)_2.H_2O$	PEG-400	-	65
9	$[RuCl_2(p$-cymene$)]_2$(5)	$Cu(OAc)_2.H_2O$	PEG-400	-	65
10	-	$Cu(OAc)_2.H_2O$	PEG-400	-	-
11	-	$Cu(OAc)_2$	DMF	-	-
12[e]	$[RuCl_2(p$-cymene$)]_2$(5)	$Cu(OAc)_2$	PEG-400	0	13
13[e]	$Pd(OAc)_2$(10)	$Cu(OAc)_2$	DMF	0	0

[a]Reaction conditions: **1e** (0.452 mmol), **2a** (0.452 mmol), catalyst, oxidant (0.3 equiv.) and solvent (3 mL) at 100 °C for 12 h. [b]Isolated yields. [c]0.5 equiv. of $Cu(OAc)_2$ is used. [d]1.0 equiv. of TBAB is used as additive. [e]The reaction was performed for 10 h. [e]N_2 balloon used as oxidant.

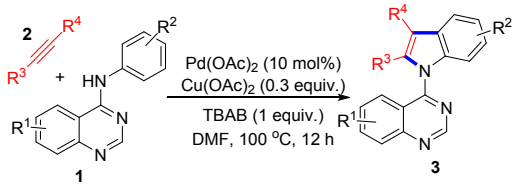
The use of Ru-catalyst, e.g. $[RuCl_2(p$-cymene$)]_2$ in the presence of $Cu(OAc)_2$ is well documented for the oxidative C–H activation/annulation.[13] We utilized the same catalyst, in the presence of $Cu(OAc)_2$ (1.0 equiv) in DMF, to afford **3ea** in 28% yield along with a new product **4ea** that was thought to be formed via the *peri* C–H bond activation/annulation of quinazoline moiety[14] (Table 1, entry 5). Thus the conditions were varied to establish the optimum reaction conditions for the *peri* C–H bond activation/annulation. When the reaction was performed in the absence TBAB, the desired product **3ea** was obtained in 35% yield along with *peri* C–H bond annulated product i.e. pyridoquinazoline (**4ea)** in 30% yield (Table 1, entry 6). After switching the solvent from DMF to PEG-400, the chemoselectivity of the product was changed drastically, giving the *peri* C–H bond annulated product (**4ea)** as the sole product in 62% yield (Table 1, entry 7). The yield was decreased to 55% when H_2O was used as the solvent instead of PEG-400 (Table 1, entry 8). Among the other solvents tested the 1,4-dioxane, toluene and DCE (Table S1, entries 13–15, ESI) led to poor selectivity and substrate conversion. Switching the oxidant from $Cu(OAc)_2$ to $Cu(OAc)_2.H_2O$ increased the yield of **4ea** to 65% (Table 1, entry 9). The yield decreased significantly when AgOAc or $AgCO_3$ or $AgNO_3$ was used as an oxidant (Table S1, entries 16-18, ESI). When the amount of the catalyst, reaction temperature and time was reduced or increased, the yield of **4ea** was affected (Table S1, entries 19-24, ESI). No annulated product was formed in the absence of Ru and Pd catalyst (Table 1, entry 10-11). Finally, the *N*-phenyl *ortho* C–H bond of quinazolin-4-amines with alkyne was optimized using 10 mol% of Pd catalyst to afford **3ea** in 68% yield (Table 1, entry 4), while the annulation through *peri* C–H bond was optimized using 5 mol % of Ru catalyst to obtain **4ea** in 65% yield (Table 1, entry 9). When the reaction was performed in the presence of Pd/Ru catalyst under N_2 atmosphere, the expected products **3ea** and **4ea** was either not formed or obtained in poor yields (Table 1, entry 12-13) indicating participation of aerial O_2 in this reaction.

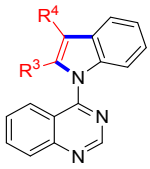
After establishing the optimized reaction conditions for selective annulation of *N*-phenylquinazolin-4-amine, the scope of the reaction of various quinazolin-4-amines with alkynes was examined. As shown in Scheme 1, Pd-catalysed selective annulation of *ortho* C–H bond of *N*-aryl ring of *N*-phenylquinazolin-4-amine with alkynes proceeded well to give the desired products irrespective of substitution patterns on the *N*-aryl ring of quinazoline. The *N*-aryl ring of quinazoline containing electron-donating substituents like Me– (**3ba**, **3bb**, **3bc**, **3bd, 3be, 3ca, 3da**, **3ja** and **3ka**), MeO– (**3ea**, **3eb**, and

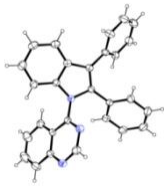
3ed) and electron-withdrawing substituents such as Cl– (**3fa** and **3fb**), Br– (**3ga** and **3gb**), CF_3 – (**3ha**), and NO_2– (**3ia**) provided the corresponding annulated products in good to moderate yields (Table 2). It was observed that the quinazoline withelectron-donating substituent Me– (**3ja**) and electron-withdrawing group Cl– (**3ka**) were well tolerated under these reaction conditions and the reaction proceeded smoothly to give the corresponding derivatives in good yields. In case of quinazoline with two electron-donating groups (**1l**), the formation of expected product (**3la**) was not observed.

Next, we tested the feasibility of this Pd-catalysed selective annulation reaction with a wide range of alkynes **2a–f**. The reaction was compatible with a variety of substituents at the *para* position on the benzene rings of internal alkynes, such as electron-donating Me– (**3ab**, **3bb**, **3eb**, **3fb** and **3gb**) and MeO– (**3ac** and **3bc**) and electron-withdrawing F– (**3ad**, **3bd** and **3ed**) groups. These alkynes could smoothly react with *N*-phenylquinazolin-4-amine (**1**) to afford the corresponding annulated products in good to moderate yields. The alkyne possessing a strong electron withdrawing NO_2 at the *para* position on the benzene rings failed to provide the desired product (**3ag**). Gratifyingly, a heterocyclic thiophene derivative also served as a suitable substrate and afforded **3ae** and **3be** in satisfactory yields. The reaction even worked with aliphatic internal alkynes to give the desired product (**3af**) in good yields.

Table 2 Pd-catalyzed synthesis of indole-quinazoline *via ortho* C–H functionalization[a,b,c]

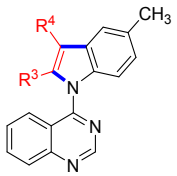




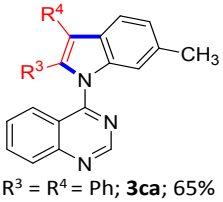


3aa

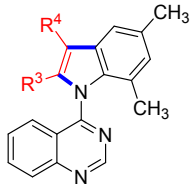
$R^3 = R^4$ = Ph; **3aa**; 65%
$R^3 = R^4$ = *p*-MeC_6H_4; **3ab**; 65%
$R^3 = R^4$ = *p*- $OMeC_6H_4$; **3ac**; 66%
$R^3 = R^4$ = *p*- FC_6H_4; **3ad**; 62%
$R^3 = R^4$ = 2-thienyl; **3ae**; 60%
$R^3 = R^4 = CH_2CH_3$; **3af**; 62%
$R^3 = R^4$ = *p*- $NO_2C_6H_4$; **3ag**; 0%



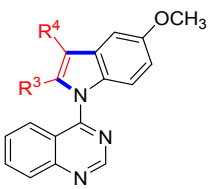
$R^3 = R^4$ = Ph; **3ba**; 64%
$R^3 = R^4$ = *p*-MeC_6H_4; **3bb**; 65%
$R^3 = R^4$ = *p*-$OMeC_6H_4$; **3bc**; 60%
$R^3 = R^4$ = *p*- FC_6H_4; **3bd**; 64%
$R^3 = R^4$ = 2-thienyl; **3be**; 59%



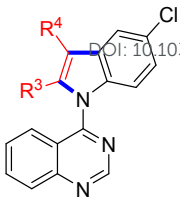
$R^3 = R^4$ = Ph; **3ca**; 65%



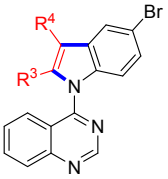
$R^3 = R^4$ = Ph; **3da**; 63%



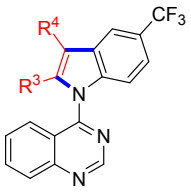
$R^3 = R^4$ = Ph; **3ea**;68%
$R^3 = R^4$ = *p*-MeC_6H_4; **3eb**; 61%
$R^3 = R^4$ = *p*- FC_6H_4; **3ed**; 63%



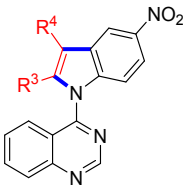
$R^3 = R^4$ = Ph; **3fa**; 65%
$R^3 = R^4$ = *p*-MeC_6H_4; **3fb**; 63%



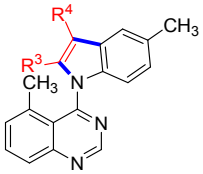
$R^3 = R^4$ = Ph; **3ga**; 68%
$R^3 = R^4$ = *p*-MeC_6H_4; **3gb**; 67%



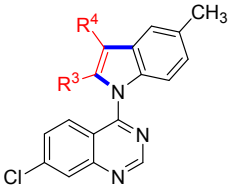
$R^3 = R^4$ = Ph; **3ha**; 62%



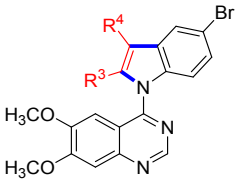
$R^3 = R^4$ = Ph; **3ia**; 55%



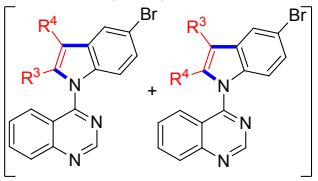
$R^3 = R^4$ = Ph; **3ja**; 64%



$R^3 = R^4$ = Ph; **3ka;** 65%



$R^3 = R^4$ = Ph; **3la**; 0%



R^3 =Ph, R^4 = *p*-MeC_6H_4; **3gh+3gh'** (1:1)[c]; 65%

[a]Reaction conditions: **1** (0.452 mmol), **2** (0.452 mmol), $Pd(OAc)_2$ (0.045 mmol), $Cu(OAc)_2$ (0.3 equiv.), TBAB (0.452 mmol) DMF (3 mL), 100 °C, 12 h. [b]Isolated yields. [c]exclusive chemoselectivity was observed, [d]Ratio of the regioisomers was determined by ^{1}H NMR.

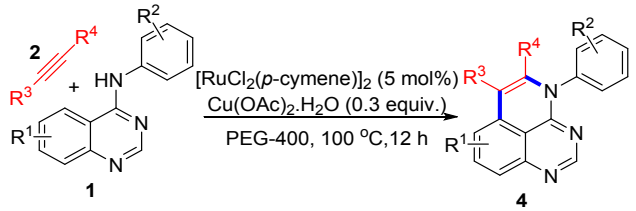
The unsymmetrical alkyne **2f** reacted under these conditions to afford a mixture of two regioisomeric products, i.e. **3gh** and **3gh'** in the ratio of 1:1 (65% yield). Since the R_f values were too close, the separation and isolation of individual isomers were quite difficult. Nevertheless, the structure of the **3aa** was further confirmed by X-ray crystallography.[14]

The oxidative annulations of various *N*-phenylquinazolin-4-amines (**1**) with internal alkynes (**2**) were also investigated under the Ru-catalyst for the construction of pyrido[2,3,4-de]quinazolines (**4**) through *peri* C–H annulation/functionalization as shown in Table 3. The *peri* C–H annulations of *N*-phenylquinazolin-4-amines having electron-donating Me– (**4ba**, **4bc**), MeO– (**4ea**, **4ec**) and electron-withdrawing Cl– (**4fa**, **4fb**), Br– (**4ga**), CF_3 (**4ha**) substituents on

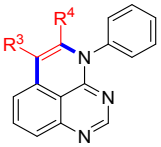
View Article Online
DOI: 10.1039/D0OB00318B

the *N*-aryl ring proceeded with high selectivity to produce pyrido[2,3,4-*de*]quinazoline derivatives in good yields. Both the electron-donating Me– (**4ab**, **4fb** and **4kb**), MeO– (**4ac**, **4bc** and **4ec**) and electron-withdrawing F– (**4ad**) groups at the *para*-position on the benzene rings of internal alkynes were well accommodated and gave in good yields. Further, quinazoline with electron-withdrawing group Cl– (**4ka** and **4kb**) were found to furnish good yields. Notably, quinazoline with two electron-donating groups (**1l**) also provided desired product **4la** in moderate yield. Further, the reaction of **1a** with a terminal alkyne i.e phenyl acetylene in the presence of Ru catalyst was examined. However, formation of no product was observed in this case indicating that the terminal alkyne was ineffective under the reaction conditions employed.

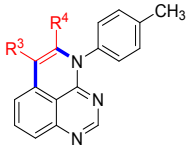
Table 3 Ru-catalyzed synthesis of triphenyl-4*H*-pyrido[2,3,4-*de*]quinazolines *via peri* C–H functionalization[a,b,c]



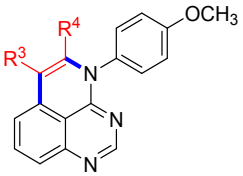
1 4



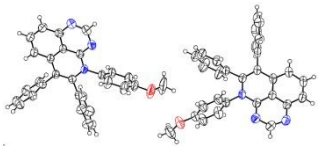
$R^3 = R^4$ = Ph; **4aa**; 65%
$R^3 = R^4$ = *p*-MeC_6H_4; **4ab**; 63%
$R^3 = R^4$ = *p*- $OMeC_6H_4$; **4ac**; 62%
$R^3 = R^4$ = *p*- FC_6H_4; **4ad**; 65%
$R^3 = R^4 = CH_2CH_3$; **4af**; 60%



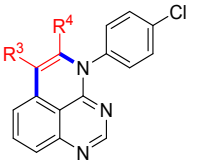
$R^3 = R^4$ = Ph; **4ba**; 65%
$R^3 = R^4$= *p*- $OMeC_6H_4$; **4bc**; 60%



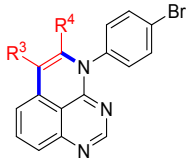
$R^3 = R^4$ = Ph; **4ea**; 65%



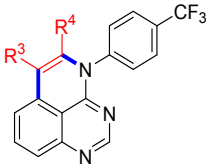
4ea



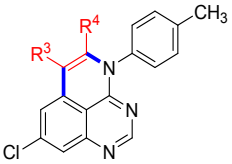
$R^3 = R^4$ = Ph; **4fa**; 63%
$R^3 = R^4$ = *p*- MeC_6H_4; **4fb**; 61%



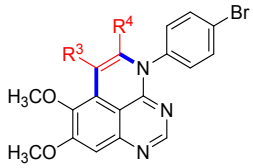
$R^3 = R^4$ = Ph; **4ga**; 63%



$R^3 = R^4$ = Ph; **4ha**; 60%



$R^3 = R^4$ = Ph; **4ka**; 64%
$R^3 = R^4$ = *p*- MeC_6H_4; **4kb**; 60%

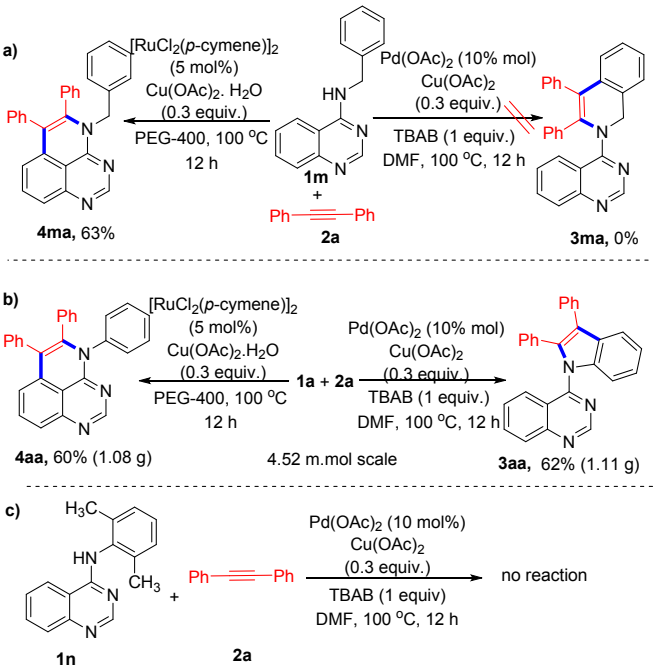


$R^3 = R^4$ = Ph; **4la**; 55%

[a]Reaction conditions: **1** (0.452 mmol), **2** (0.452 mmol), $[RuCl_2(p\text{-cymene})]_2$ (0.022 mmol), $Cu(OAc)_2.H_2O$ (0.3 equiv.), PEG-400 (3 mL), 100 °C, 12 h. [b]Yields of isolated products are given, [c]exclusive chemoselectivity was observed.

Encouraged by the above results, we explored the catalyst and solvent controlled divergent C–H functionalization of *N*-benzylquinazolin-4-amine **1m** with phenyl substituent internal acetylene **2a** using Ru-catalyst and the desired *peri* annulated products, **4ma** was obtained in 63% yield. Formation of *ortho* C–H functionalized product (**3ma**) was not observed using Pd-catalyst with same substrates (Scheme 2a).

In order to demonstrate the scale-up potential of our method, a gram-scale experiment involving the Pd catalyzed annulation was performed employing **1a** and **2a** as model substrates; the product **3aa** was obtained in 62% (1.11 g) yield (Scheme 2b). The 4.52 mmol scale reaction of **1a** and **2a** under Ru catalyst could give the product **4aa** in 60% yield (1.08 g) (Scheme 2b). To gain some insights about the reaction mechanism, the following control experiment was performed (Scheme 2c). The *N*-(2,6-dimethylphenyl)quinazolin-4-amine (**1n**) was used under Pd catalysis and no reaction with **2a** was observed, and **1n** was recovered in 92%, indicating that the *ortho* C–H of *N*-aryl ring of quinazolin-4-amine plays a key role for the synthesis of indole-quinazoline derivatives (3) (Scheme 2c).

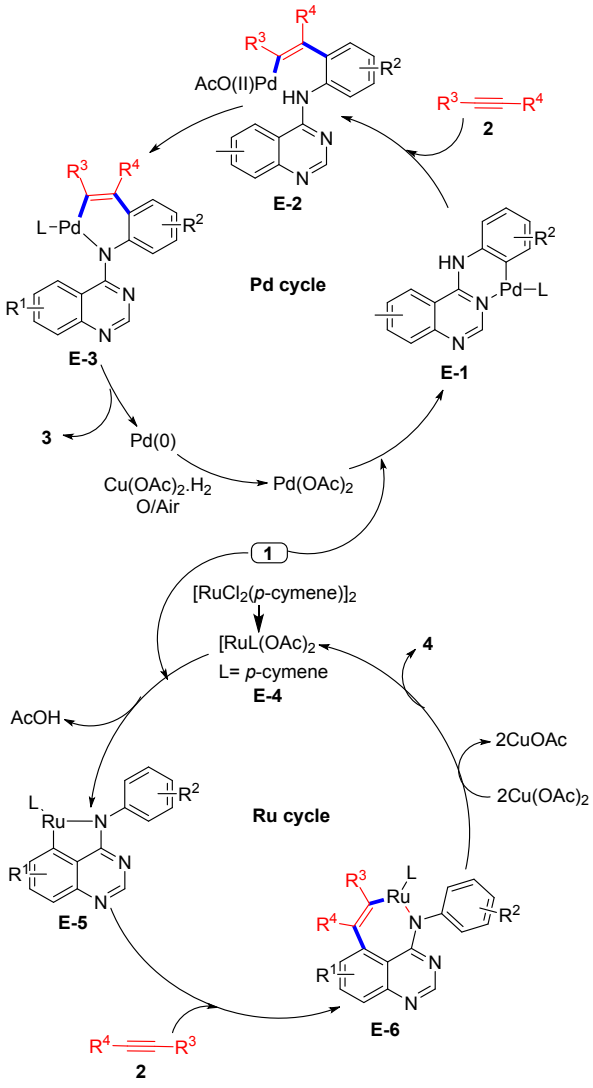


Scheme 2 Synthetic elaboration, gram-scale and control experiments.

The reasons behind the site selectivity may be due to the formation of kinetically favoured six-membered metallacycle **A** (Scheme **1**) in the presence of Pd catalyst and the formation

of five-membered metallacycle **B** (Scheme **1**) when Ru catalyst was used.[6a,13]

Based on these observations and the previous reports, [13, 15, 16] the mechanism for this regioselective functionalization of C–H bonds are proposed in Scheme 3. Firstly, $Pd(OAc)_2$ reacts with **1** through electrophilic aromatic palladation to form intermediate **E-1**, which subsequently interacts with alkyne **2** to generate a vinylic palladium(II) intermediate **E-2**. The six-membered palladacycle **E-3** can be formed from **E-2** through 2nd electrophilic aromatic palladation involving the interaction of proximate "NH" group with the Pd(II) species. Subsequent reductive elimination affords the corresponding 4-(1*H*-indol-1-yl)quinazoline product (**3**) along with Pd(0) complex that can be oxidized to regenerate the active palladium acetate complex in the presence of oxidant. It is known that TBAB acts as a stabilizer for Pd catalyst avoiding the fast agglomerization and thus allows the progress of the desired reaction.[17]



Scheme 3 Plausible reaction mechanism

In case of *peri*-quinazoline C-H bond activation, Ru-catalyzed cycle starts by forming the active catalyst $RuL(OAc)_2$ (**E-4**) *via*, the ligand exchange of $[RuCl_2(p\text{-cymene})]_2$ with an acetate ion. The *peri* C–H bond activation of *N*-phenylquinazolin-4-amines **1** involves the formation of five membered ruthenacycle **E-5** followed by insertion of alkyne moiety **2** into the Ru–C bond to furnish the ruthenium intermediate **E-6**. Finally, a reductive elimination leading to expected *peri* annulated product (**4**) with the generation of Ru(0) species followed by its oxidation to Ru(II) completes the cycle. The Ru(0) species is oxidized to the active Ru(II) catalyst in the presence of $Cu(OAc)_2.H_2O$ (Scheme 3).

Conclusions

In summary, we have demonstrated for the first time, the differential and regioselective functionalization of C–H bonds of *N*-aryl substituted quinazolin-4-amines *via* oxidative annulation with internal alkynes. The *ortho* C–H bonds functionalization was favoured by Pd-catalyst in DMF, whereas the *peri* C–H bond functionalization was favoured by Ru-catalyst in PEG. By using these two strategies we have synthesized a variety of indolquinazolines and pyridoquinazolines in good to moderate yields with high chemoselectivity. This catalyst-switched annulation is quite interesting and may become useful method for the construction of fused *N*-heterocycles.

Acknowledgements

KSK thanks the University Grants Commission (UGC), New Delhi, for a faculty position under FRP. We also thank CSIR [02(0036)/19/EMR-II], New Delhi and OU-DST-PERSE-II for funding this project. PKN thanks CSIR, New Delhi for a fellowship.

Conflicts of interest

The authors confirm that this article content has no conflict of interest.

Notes and references

1 (a) G. Dyker, Handbook of C–H Transformations. Applications in Organic Synthesis, Wiley-VCH, Weinheim, Germany, 2005; (b) S. R. Neufeldt, M. S. Sanford, *Acc. Chem. Res.,* 2012, **45**, 936–946; (c) D. A. Colby, A. S. Tsai, R. G. Bergman and J. A. Ellman, *Acc. Chem. Res.*,2012, **45**, 814–825; (d) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.,* 2012, **112**, 5879–5918; (e) G. Rouquetand N. Chatani, *Angew. Chem. Int. Ed.,* 2013, **52**, 11726–11743; (f) J. Li, S. De Sarkar and L. Ackermann, *Top. Organomet. Chem.*, 2015, **55**, 217–257; (g) J. F. Hartwig, *J. Am. Chem. Soc.,* 2016, **138**, 2–24; (h) J. F. Hartwig, *Acc. Chem. Res*., 2017, **50**, 549–555 (i) T. Xu, F. Sha and H. Alper, *J. Am. Chem. Soc*., 2016, **138**, 6629–6635; (j) F. Jiang, D. Zhao, X. Yang, F.-R. Yuan, G.-J. Mei and F. Shi, *ACS Catal*., 2017, **7**, 6984–6989.

2 (a) D. A. Colby, R. G. Bergman and J. A. Ellman, *Chem. Rev.,* 2010, **110**, 624–655; (b) O. Daugulis, H. -Q. Do and D. Shabashov, *Acc. Chem. Res.,* 2009, **42**, 1074–1086; (c) T. W. Lyons and M. S. Sanford, *Chem. Rev.,* 2010, **110**, 1147–1169; (d) K. M. Engle, T. -S. Mei, M. Wasaand J. -Q. Yu, *Acc. Chem. Res.,* 2012, **45**, 788–793; (e) C. S. Yeung and V. M. Dong, *Chem. Rev.,* 2011, **111**, 1215–1292; (f) D. Leow, G. Li, T. -S. Mei and J. -Q. Yu, *Nature,* 2012, **486**, 518–522; (g) S.Tani,T. N. Uehara, J. Yamaguchi and K. Itami, *Chem. Sci.,* 2014, **5**, 123–135.

3 (a) Y. Feng and G. Chen, *Angew. Chem. Int. Ed.,* 2010, **49**, 958–961; (b) W. R. Gutekunstand P. S. Baran, *Chem. Soc. Rev.,* 2011, **40**, 1976–1991; (c) L. Ackermann, *Chem. Rev*., 2011, **111**, 1315–1345; (d) H. M. L. Davies, J. Du Bois and J.-Q. Yu, *Chem. Soc. Rev*., 2011, **40**, 1855–1856; (e) L. Mc Murray, F. O'Hara and M. J. Gaunt, *Chem. Soc. Rev*., 2011, **40**, 1885–1898; (f) S. H. Cho, J. Y. Kim, J. Kwak and S. Chang, *Chem. Soc. Rev*., 2011, **40**, 5068–5083; (g) C. -L. Sun, B. -J. Li and Z. -J. Shi, *Chem. Rev.,* 2011, **111**, 1293–1314; (h) J. Wencel-Delord, T. Dröge, F. Liu and F. Glorius, *Chem. Soc. Rev*., 2011, **40**, 4740–4761; (i) B. -J. Li and Z. -J. Shi, *Chem. Soc. Rev*., 2012, **41**, 5588–5598; (j) J. Wencel-Delordand F. Glorius, *Nat. Chem*., 2013, **5**, 369–375; (k) A. V. Gulevich, A. S. Dudnik, N. Chernyakand V. Gevorgyan, *Chem. Rev*., 2013, **113**, 3084–3213; (l) J. Chen, Q. Pang, Y. Sun, X. Li, *J. Org. Chem.,* 2011, **76**, 3523–3526; (m) F. Xu, Y. J. Li, C. Huang, H. C. Xu, *ACS Catal.,* 2018, **8**, 3820–3824; (n) R. Mei, J. Koeller, L. Ackermann, *Chem. Commun.,* 2018, **54**, 12879–12882.

4 (a) K. C. Nicolaou, J. A. Pfefferkorn, A. J. Roecker, G. Q. Cao, S. Barluenga and H. J. Mitchell, *J. Am. Chem. Soc*., 2000, **122**, 9939–9953; (b) S. A. Shakoor, S. Kumari, S. Khullar, S. K. Mandal, A. Kumar and R. Sakhuja, *J. Org. Chem*., 2016, **81**, 12340–12349; (c) A. Modi, P. Sau, N. Chakraborty, B. K. Patel, *Adv. Synth. Catal*., 2019, **361**, 1368–1375; (D) V. Lanke, K. R. Bettadapur and K. R. Prabhu, *Org. Lett*., 2016, **18**, 5496–5499; (e) J. R. Huckins, E. A. Bercot, O. R. Thiel, T. L. Hwang and M. M. Bio, *J. Am. Chem. Soc*., 2013, **135**, 14492–14495; (f) S. Li, H. Ji, L. Cai, G. Li, *Chem. Sci.,* 2015, **6**, 5595– 5600.

5 (a) R. Simayi, S. M. Gillbard, W. B. Cross, E. G. Hope, K. Singha and G. A. Solan, *Dalton Trans.*, 2018, **47**, 11680-11690; (b) K. M. Engle and J.-Q. Yu, *J. Org. Chem*., 2013, **78**, 8927–8955; (c) X. -C. Wang, W. Gong, L. -Z. Fang, R. -Y. Zhu, S. Li, K. M. Engle and J. -Q. Yu, *Nature,* 2015, **519**, 334–338.

6 J. D. Dooley, S. R. Chidipudiand H. W. Lam, *J. Am. Chem. Soc*., 2013, **135**, 10829–10836.

7 Á. M. Martínez, J. Echavarren, I. Alonso, N. Rodríguez, R. G. Arrayásand J. C. Carretero, *Chem. Sci*., 2015, **6**, 5802–5814.

8 (a) G. Tan, L. Zhang, X. Liao, Y. Shi, Y. Wu, Y. Yang and J. You, *Org. Lett.*, 2017, **19**, 4830–4833; (b) A. C. Shaikh, D. R. Shinde and N. T. Patil, *Org. Lett*., 2016, **18**, 1056–1059; (c) S. Lee, S. Mah and S. Hong, *Org. Lett*., 2015, **17,** 3864–3867.

9 For recent selected examples, see: (a) Y. Li, F. Xie and X. Li, *J. Org. Chem*., 2016, **81**, 715–722; (b) S. Lee, S. Mahand S. Hong, *Org. Lett*., 2015, **17**, 3864–3867; (c) Y. Chi, W. X. Zhang, Z. Xi, *Org. Lett.,* 2014, **16**, 6274–6277; (d) R. J. Phipps and M. J. Gaunt, *Science,* 2009, **323**, 1593–1597; (e) G. L. Tolnai, S. Ganss, J. P. Brand and J. Waser, *Org. Lett*., 2013, **15**, 112–115; (f) C. Cheng and J. F. Hartwig, *Science* 2014, **343**, 853–857; (g) A. M. Wagner, A. J. Hickman and M. S. Sanford, *J. Am. Chem. Soc*., 2013, **135**, 15710–15713; (h) V. K. Tiwari, N. Kamal and M. Kapur, *Org. Lett*., 2017, **19**, 262–265.

10 (a) R. Dalpozzo, *Chem. Soc. Rev*., 2015, **44**, 742–778; (b) H. Wu, Y.-P. He and F. Shi, *Synthesis*, 2015, **47**, 1990–2016; (c) J.-B. Chen and Y.-X. Jia, *Org. Biomol. Chem*., 2017, **15**, 3550–3560; (d) Y. C. Zhang, F. Jiang and F. Shi, *Acc. Chem. Res*., 2019, **53**, 425–446; (e) J. P. Michael, *Nat. Prod. Rep.,* 2008, **25**, 139–165; (f) J. Stöckigt, S. Panjikar, *Nat. Prod. Rep*. 2007, **24**, 1382–1400; (g) L. F. Tietze, Y.-F. Zhou, *Angew. Chem., Int. Ed.* 1999, **38**, 2045–2047.

11 (a) K. S. Kumar, S. R. Meesa and P. K. Naikawadi, *Org. Lett*., 2018, **20**, 6079–6083; (b) K. S. Kumar, P. K. Naikawadi, R. Jatoth, R. Dandela, *Org. Biomol. Chem*., 2019, **17**, 7320–7324; (c) K. S. Kumar, P. K. Naikawadi, B. Rajesham and D. Rambabu, *New J. Chem*., 2019, **43**, 4333–4337.

12 (a) K. S. Kumar, B. Bhaskar, M. S. Ramulu, N. P. Kumar, M. A. Ashfaq and M. Pal, *Org. Biomol. Chem*., 2017, **15**, 82–87; (b) K. S. Kumar, M. S. Ramulu, B. Rajesham, N. P. Kumar, V. Voora and R. K. Kancha, *Org. Biomol. Chem.,* 2017, **15**, 4468–4476.

13 (a) M. Shankar, K. Ghosh, K. Mukherjee, R. K. Ritand A. K Sahoo, *Org. Lett*., 2018, **20**, 5144–5148; (b) S. Allu and K. C. K. Swamy, *Adv. Synth. Catal*., 2015, **357**, 2665-2680; (c) Y. Tokoro, K. Sugita and S. -i. Fukuzawa, *Chem. Eur. J*., 2015, **21**, 13229–13232; (d) H. Zhao, T. Zhang, T. Yan and M. Cai, *J. Org. Chem*., 2015, **80**, 8849–8855.

14 The CIF files have been deposited with the Cambridge Crystallographic Data centre as supplementary publication no. CCDC 1949441 **(4ea)** and 1949446 **(3aa).**

15 M. Shankar, T. Guntreddi, E. Ramesh and A. K. Sahoo, *Org. Lett.,* 2017, **19**, 5665–5668.

16 (a) Z. Shi, S. Ding, Y. Cui and N. Jiao, *Angew. Chem. Int. Ed*., 2009, **48**, 7895–7898; (b) Z. Shi, C. Zhang, S. Li, D. Pan, S. Ding, Y. Cui and N. Jiao, *Angew. Chem. Int. Ed*., 2009, **48**, 4572-4576.

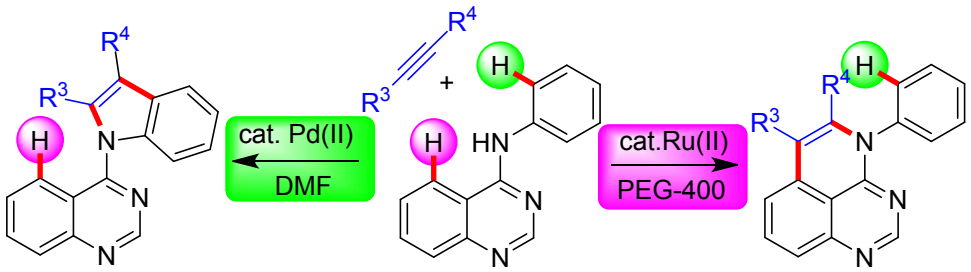
17 (a) M. T. Reetz, E. Westermann, *Angew. Chem. Int. Ed.,* 2000, **39**, 165–168; (b) J. Yu, Z. Hong, X. Yang, Y. Jiang, Z. Jiang, W. Su, *Beilstein J. Org. Chem.,* 2018, **14**, 786–795.

A table of contents entry

View Article Online
DOI: 10.1039/D0OB00318B

Catalyst and solvent switched divergent C–H functionalization: oxidative annulation of N-aryl substituted quinazolin-4-amine with alkynes

Siddi Ramulu Meesa, Praveen Kumar Naikawadi, Kishan Gugulothu, K. Shiva Kumar*



Catalyst and solvent controlled *ortho*/*peri* site-selective oxidative annulation of C–H bonds of *N*-aryl substituted quinazolin-4-amines with internal alkynes.