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Ruthenium(II)-catalyzed C–H activation/C–N bond formation *via in situ* generated iminophosphorane as the directing group: construction of annulated pyridin-2(1*H*)-ones†

Rajesh K. Arigela,[a] Ravi Kumar,[ab] Trapti Joshi,[c] Rohit Mahar[c] and Bijoy Kundu*[ab]

We describe an efficient and straightforward synthesis of annulated pyridin-2(1*H*)-ones following condensation of acyl azides with internal alkynes *via* the ruthenium-catalyzed *ortho* C–H bond activation. The reaction in DCE proceeds *via in situ* generation of iminophosphoranes as directing group-coordination of Ru with N-atom-*ortho* cyclometallation-insertion of an alkyne into the Ru–C bond-protonation-reductive elimination in a domino sequence. The role and stability of *in situ* generated iminophosphorane and ruling out the possibility for the benzamide involvement was established using ^{1}H and ^{31}P NMR experiments.

In recent years, the directing group (DG) concept[1] for the *ortho* C–H activation/functionalization has emerged as a powerful approach for *de novo* construction of a wide variety of annulated heterocycles of medicinal significance. The directing groups generally comprise functional groups (FG) with abilities to act as versatile ligands to transition metals and form *ortho*-cyclometallated complexes for smooth functionalization at the *ortho* C–H position. Interestingly, in organic chemistry, besides recent application of functional groups as DGs, they traditionally remained in use for a wide variety of selective transformations. Report exploiting the dual ability of FG, by transforming a non-directing functional group into an *in situ* DG is scarce.[2] Such a strategy would provide options to proceed with a selective transformation of a functional group either into other functionalities or into a DG for the *ortho* C–H activation.

Among plethora of applications reported for the synthesis of heterocycles utilizing the DG concept, synthesis of 1-(2*H*)-isoquinolones in a single step from arenes bearing a directing group attracted our attention. The core structure has drawn much attention owing to its ubiquity in plant alkaloids,[3] and many biologically active natural products[4] and due to its remarkable pharmacological importance ranging from anticancer, antihypertensive,[5] to topoisomerase I inhibitor activities.[6] A careful literature survey revealed synthesis of 1-(2*H*)-isoquinolones *via* oxidative insertion of internal alkyne across arenes with directing groups comprising oximes (CONHOMe, CONHOPiv, CONHOH, CONMeSOPh) and nitriles (CN) in the presence of Rh-, Ru-assisted catalysts (Fig. 1).[7]

Ironically, investigations leading to the direct synthesis of 1-(2*H*)-isoquinolones from primary aryl carboxamides either failed to undergo oxidative annulation with internal alkynes or furnished undesired tricyclic amides *via* double oxidative insertion of internal alkynes.[7a,8a,b] Pursuing our interest in heterocycles based on privileged structures,[9] we were interested in the application of *in situ* generated iminophosphoranes as a DG using less expensive Ru catalyzed oxidative conditions. The motivation for the use of iminophosphoranes as DG stemmed from several reports[10] demonstrating regioselective palladation of keto-stabilized iminophosphoranes [$Ph_3P{=}NC(O)Ar$] *via ortho* C–H activation. For the *in situ* generation of iminophosphoranes as a DG under mild reaction conditions, we envisioned that aryl acyl azides with poor

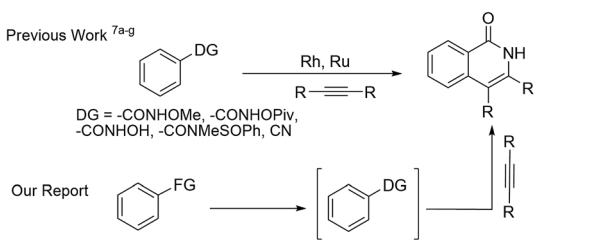

Fig. 1 Ours, and literature strategies for the synthesis of 1-(2*H*)-isoquinolones *via ortho* C–H activation/functionalization from arenes bearing DGs and internal alkynes.

[a]*Medicinal & Process Chemistry Division, CSIR-Central Drug Research Institute, B.S. 10/1, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow, 226031, India. E-mail: bijoy_kundu@yahoo.com*

[b]*Academy of Scientific and Innovative Research, New Delhi, 110001, India*

[c]*Sophisticated Analytical Instrumental Facility, CSIR-Central Drug Research Institute, Lucknow, 226031, India*

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directing group abilities could be the ideal choice as the precursor (Fig. 2a).

Recently, acyl azides has been employed as FG for the *ortho* functionalization of a DG carrying arene affording N-substituted amides *via* either C–N or C–O bond formation[11] (Fig. 2b). Other application includes transformation to a heterocycle[12] without employing DG concept. To the best of our knowledge, application of *in situ* generated iminophosphoranes as DG leading to *ortho* C–H activation/functionalization has not been reported. In this communication, we report Ru-catalyzed C–H activation/C–N bond formation involving aryl acyl azides and internal alkynes to afford 1-(2*H*)-isoquinolones in one pot.

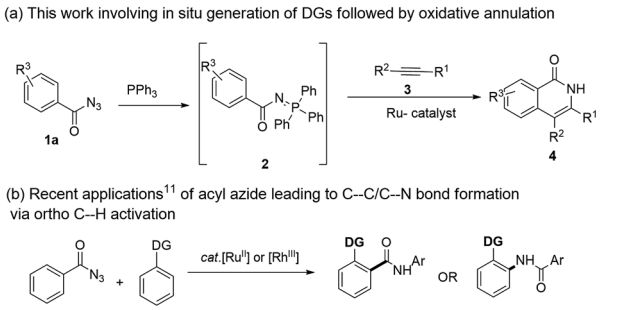
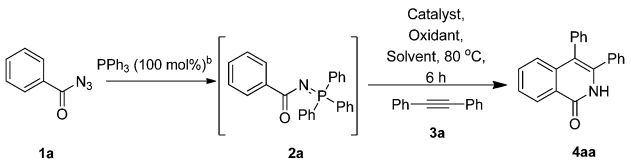


Fig. 2 Dual application of acyl azides for *in situ* generation of DGs and for functionalization of molecules *via ortho* C–H activation.

We commenced our studies by treating benzoyl azide **1a** with unactivated internal alkyne **3a** in the presence of (1.0 equiv.) TPP (triphenylphosphine) in DCE without the addition of Ru catalyst (Table 1). The reaction failed to give the desired product **4aa** instead resulted in a corresponding iminophosphorane **2a** as the only product following the Staudinger reaction[13] (entry 1). Next, we carried out the same reaction in the presence of $[Ru(p\text{-cymene})Cl_2]_2/AgSbF_6/Cu(OAc)_2\cdot H_2O$ mixture which resulted in the formation of a desired product **4aa** albeit in 32% isolated yield (entry 2) with recovery of **2a** in 26% isolated yield. Removing $AgSbF_6$ as an additive raised the isolated yield of **4aa** to 42% (entry 3) while raising the loading of the oxidant $Cu(OAc)_2\cdot H_2O$ from 20 mol% to 100 mol% selectively afforded **4aa** in 86% isolated yield (entry 4). Carrying out control experiment in the absence of Cu-salt resulted in the recovery of **2a** with no formation of **4aa** (entry 5). Replacing $Cu(OAc)_2\cdot H_2O$ with other oxidants like $K_2S_2O_8$, *t*-BuOOH and $CuBr_2$ reactions failed to give **4aa** (entry 6–8). Similarly, replacing Ru- with Rh- and Pd-catalysts failed to initiate the reaction with the recovery of **2a** (entry 9–12).

Next, we studied the affect of polar and nonpolar solvents on the outcome of the reaction. While replacing DCE with toluene furnished a mixture of **4aa** and an iminophosphorane intermediate **2a** in 28% and 45% yields respectively (entry 13), use of THF and acetonitrile afforded **4aa** in traces (entry 14) with the recovery of **2a** in 35% yield. Indeed, introducing polar solvents had a dramatic effect and led to interesting findings. Carrying

Table 1 Optimization of reaction condition for the annulation of acyl azide **1a** with unactivated internal alkyne **3a**[a]



Entry	Catalyst (3.0 mol%)	Oxidant (mol%)	Solvent	Yield[d] **2a**/**4aa** (%)
1		$Cu(OAc)_2$ (20)	DCE	65/—
2[c]	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2$ (20)	DCE	26/32
3	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2$ (20)	DCE	22/42
4	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2$ (100)	DCE	—/86
5	$[RuCl_2(p\text{-cymene})]_2$	—	DCE	78/—
6	$[RuCl_2(p\text{-cymene})]_2$	$K_2S_2O_8$ (100)	DCE	63/NR
7	$[RuCl_2(p\text{-cymene})]_2$	*t*-BuOOH (100)	DCE	65/NR
8	$[RuCl_2(p\text{-cymene})]_2$	$CuBr_2$ (100)	DCE	68/NR
9	$Rh(PPh_3)_3Cl$	$Cu(OAc)_2$ (100)	DCE	55/NR
10	$Pd(OAc)_2$	$Cu(OAc)_2$ (100)	DCE	58/NR
11	$Pd(OAc)_2$	$K_2S_2O_8$ (100)	DCE	52/NR
12	$Pd(OAc)_2$	*t*-BuOOH (100)	DCE	38/NR
13	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2$ (100)	Toluene	45/28
14	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2$ (100)	THF,ACN	35/trace
15	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2$ (100)	MeOH	63[e,f]
16	$[RuCl_2(p\text{-cymene})]_2$	$Cu(OAc)_2$ (100)	*t*-AmOH	38[g]

[a] Reaction conditions: **1a** (1.0 equiv.), **3a** (0.8 equiv.), PPh_3 (1.0 equiv.), $[Ru(p\text{-cymene})Cl_2]_2$ (3.0 mol%), and $Cu(OAc)_2\cdot H_2O$ (100 mol%), in 5 mL DCE, 80 °C, 6 h. [b] In the absence of PPh_3 benzoyl azide underwent degradation under standard condition (with no detectable formation of **4aa**). [c] 5.0 mol% $AgSbF_6$ were used. [d] Yield of isolated products. [e] Reaction stirred for 10 h. [f] A yellow colored byproduct in ~10% yield. [g] Byproducts: benzamide in 15% yield and a yellow colored spot in 23% yield.

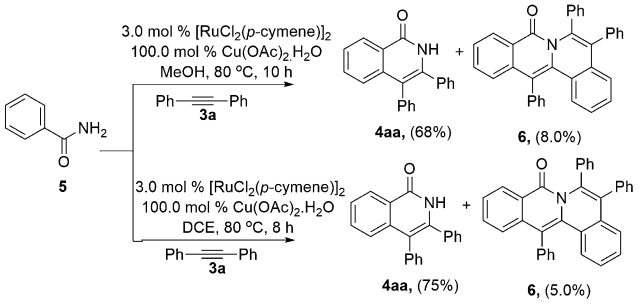
out reaction in MeOH, although made the reaction sluggish, transformation of **1a** initially afforded **2a** along with an additional intermediate on tlc. Prolonged stirring led to gradual disappearance of both the intermediates affording **4aa** along with a yellow colored byproduct **6** in 63% and ~10% isolated yields respectively (entry 15). For the characterization of the new intermediate observed in MeOH, we quenched the reaction after 5 h that resulted in the isolation of two intermediates iminophosphorane **2a** (32%) and benzamide **5** (36%) and the byproduct **6** in traces.[14]

Replacing MeOH with yet another polar solvent *t*-AmOH afforded **4aa** in reduced yield (38%) along with the isolation of benzamide **5** in 15% and the byproduct **6** in 23% yield (entry 16). Literature precedence report formation of iminophosphoranes and benzamides in polar solvents from acyl azides.[15] The yellow coloured byproduct **6** observed in polar solvents was characterized as a tricyclic compound[14] and as reported by Miura *et al.*[8a] and Xingwei Li *et al.*[8b] has been reported to be formed following the reaction of **4aa** with another molecule of internal alkyne.

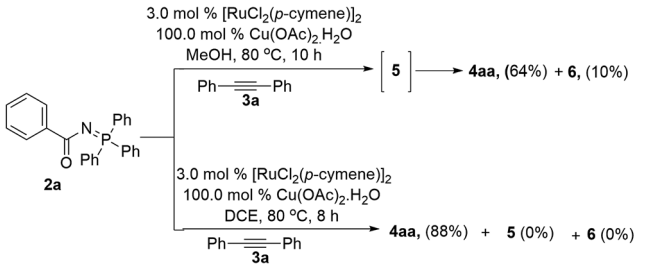
Thus, it is evident from the optimization studies that transformation of acyl azides **1a** to **4aa** is highly favored in DCE and proceeds *via in situ* generated iminophosphoranes with no formation of byproduct **6.** On the contrary, in polar solvent both iminophosphorane and benzamide are generated *in situ* and formation of **4aa** is accompanied by formation of the yellow coloured tricyclic byproduct **6** in 10–23% isolated yields (Table 1).

The involvement of intermediates **2a** and **5** in the transformation was further confirmed by treating presynthesized benzamide **5** (Scheme 1) and iminophosphorane **2a** (Scheme 2) separately with **3a** in MeOH/DCE. As is evident, selective transformation of **2a** to **4aa** occurred in higher yields in DCE, whereas formation of byproduct **6** was observed from benzamide **5** both in MeOH and DCE. The findings suggest acyl azides **1** as the best option for the synthesis of pyridin-2(1*H*)-ones over that of benzamide **5**.

Although several literature reports[7a,8a,8b] involving reaction of pre-synthesized **5** with the internal alkyne demonstrate formation of either a yellow colored tricyclic compound **6** as the major product or a benzannulated derivative[14] as a minor product with the recovery of **5**, a single report by Jeganmohan *et al.*[7g] describes formation of **4aa** from benzonitrile *via* the *in situ*



Scheme 1 Treatment of presynthesized benzamide **5** with unactivated internal alkyne **3a** in MeOH and DCE.



Scheme 2 Treatment of presynthesized iminophosphorane **2a** with unactivated internal alkyne **3a** in MeOH and DCE.

benzamide (**5**) intermediacy. This is in accordance to our observation involving transformation of **1a** to **4aa** in MeOH *via in situ* benzamide intermediacy. Furthermore, the role and stability of iminophosphoranes during the transformation in DCE and also ruling out involvement of benzamide was confirmed by ^{1}H and ^{31}P NMR experiments.[14]

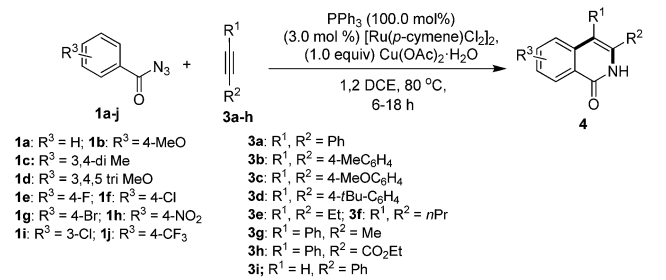
With optimized conditions in hand, we then proceeded to study the scope and limitation of the transformation in DCE. Initially, a series of benzoyl azides (**1a–j**) bearing electron-donating and -withdrawing groups (R^3) were subjected to oxidative annulation with both aliphatic and aromatic internal alkynes (**3a–h**) in DCE (Table 2).

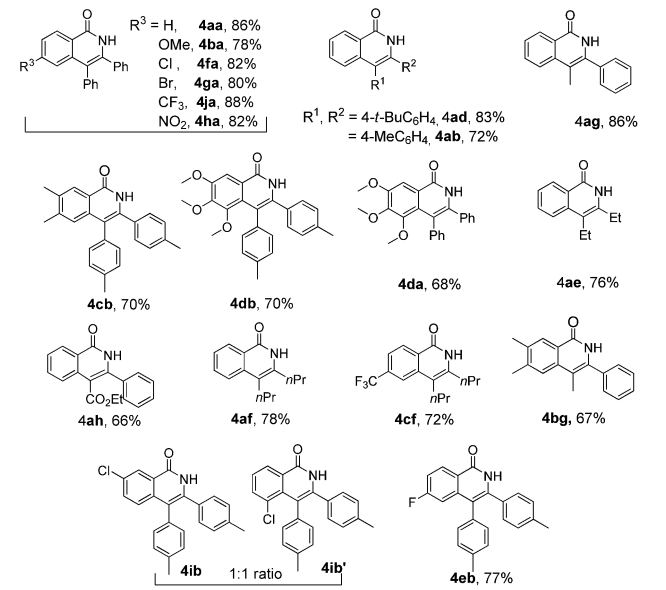
In all nineteen 1-(2*H*)-isoquinolones based on **4** were synthesized in 66–88% isolated yields. As is evident, the presence of a single electron-donating and -withdrawing groups in **1** at position 4 of the aromatic ring furnished products in >80% isolated yield with minimal variations. However, introduction of two electron-donating substituents in the aromatic ring at position 3 and 4 reduced the isolated yield to 68–70%. Among symmetrical internal alkynes replacement of R^1 and R^2 with aromatic ring bearing electron-donating groups produced corresponding **4** in relatively higher yield (**4ad**) than aliphatic chain (**4af**, **4ae**).

Employing unsymmetrical internal alkynes bearing-aliphatic/aromatic and, aromatic/COOEt moieties as R^1/R^2 furnished **4ah** and **4ag** in good to moderate yields with high regioselectivity (Table 2). Terminal alkyne failed to facilitate annulations. The versatility of methodology was demonstrated by replacing benzoyl azides with thiophene and indole-based acyl azides (**1k–n**). Treating with a variety of internal alkynes furnished 8 examples of corresponding **4** in moderate to good isolated yields (Table 3).

Based on the literature reports,[7c,7f,7g,10a,b,16] a plausible mechanism for the formation of **4aa** is depicted in Scheme 3. The ruthenium dimer precatalyst undergoes dissociation into the coordinatively unsaturated monomer in solution, which exchanges ligand with $Cu(OAc)_2 \cdot H_2O$ to form an acetate-ligated species. This metal upon coordination with N-atom of the iminophosphorane **2a** (derived from **1a**) followed by *ortho* cyclometallation afforded a five membered ruthenacycle **I** with the loss of acetic acid through an acetate-assisted mechanism. This is then accompanied by the insertion of an alkyne into the Ru–C bond to afford a seven membered ruthenacycle intermediate **II**. Finally the protonation of **II** followed by reductive

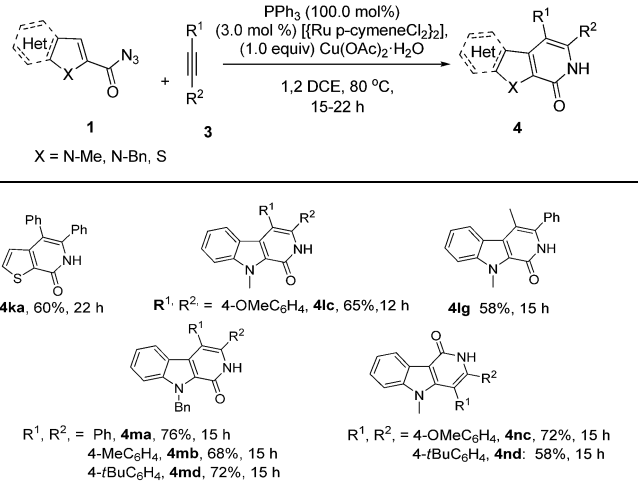
Table 2 Scope of the ruthenium-catalyzed C–H activation of acylazides with internal alkynes[a]



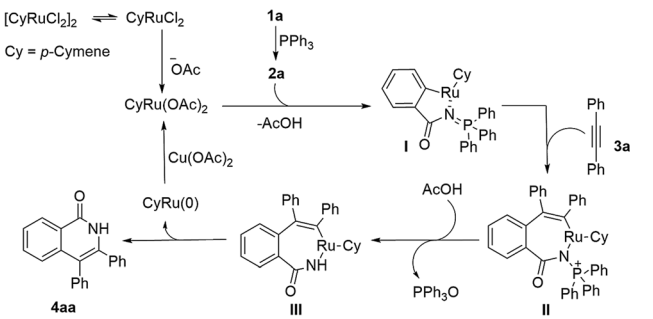


[a] Reaction condition: (1.0 equiv.) of **1**, (0.8 equiv.) of **3**, (100.0 mol%) of PPh_3, (3.0 mol%) $[Ru(p\text{-cymene})Cl_2]_2$, (100 mol%) of $Cu(OAc)_2 \cdot H_2O$ in 5 mL of DCE at 80 °C.

Table 3 Scope of the various heterocycles using the same strategy[a]



[a] Reaction condition: (1.0 equiv.) of **1**, (0.8 equiv.) of **3**, (100.0 mol%) of PPh_3, (3.0 mol%) $[Ru(p\text{-cymene})Cl_2]_2$, (1.0 equiv.) of $Cu(OAc)_2 \cdot H_2O$ in 5 mL of DCE at 80 °C.



Scheme 3 A plausible mechanism for the formation of **4aa** *via* iminophosphorane.

elimination affords **4aa** with the dissociation of triphenyl phosphine by the *in situ* generated acetic acid[16] and reduction of the ruthenium from Ru(II) to Ru(0). Latter undergoes oxidation to regenerate the catalytically active Ru(II) complex with the aid of copper oxidant.

In summary we have described a Ru-catalyzed *ortho* C–H activation and intramolecular C–N bond formation *via in situ* generated iminophosphoranes as a directing group. The synthetic protocol involves one pot condensation of acyl azides with internal alkynes leading to straightforward and efficient synthesis of a variety of annulated pyridin-2(1*H*)-ones. The salient feature of the reaction in DCE involves *in situ* generation of iminophosphorane-coordination of Ru with N-atom-*ortho* cyclometallation-insertion of an alkyne into the Ru–C bond-protonation-reductive elimination domino sequence. Further studies are in progress with application of other *in situ* generated DGs for the synthesis of heterocycles *via de novo* routes.

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