RSC Advances

Volume 1 | Number 1 | Jan 2013 | Pages 1–100

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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(1H)-ones

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We describe an efficient and straightforward synthesis of annulated pyridin-2(1H)-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 possibility for the benzamide involvement was established using ^{1}H and ^{31}P NMR experiments.
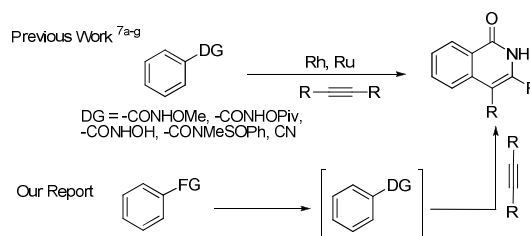
Fig 1. Ours, and literature strategies for the synthesis of 1-(2H)-isoquinolones via *ortho* C—H activation/functionalization from arenes bearing DGs and internal alkynes.

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*-cyclo-metallated 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(2H)-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-(2H)-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-(2H)-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 [Ph₃P=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 directing group abilities could be the ideal choice as the precursor (Figure 2a).

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(a) This work involving in situ generation of DGs followed by oxidative annulation
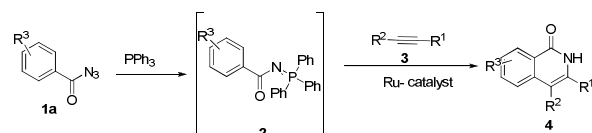
(b) Recent applications[11] of acyl azide leading to C—C/C—N bond formation
via ortho C—H activation
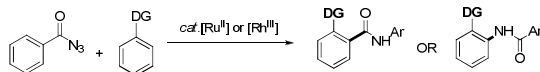
Fig 2. Dual application of acyl azides for in situ generation of DGs and for functionaliztion of molecules via *ortho* C—H activation.

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] (Figure 2b). Other application includes transformation to a heterocycle[12] without employing DG concept. To the best of our knowledge, application of in situ generated iminophopshoranes 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-(2H)-isoquinolones in one pot.

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 iminophoshorane **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*-cymene)Cl₂]₂/AgSbF₆/Cu(OAc)₂·H₂O 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 AgSbF₆ as an additive raised the isolated yield of **4aa** to 42% (entry 3) while raising the loading of the oxidant Cu(OAc)₂·H₂O 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·H₂O with other oxidants like K₂S₂O₈, *t*-BuOOH and CuBr₂ 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 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 disapearance of both the intermediates affording **4aa** along with a yellow colored byproduct **6** in 63% and ~10% isolated yields

respectively (entry 15). For the charaterization of the new intermediate obsedved in MeOH, we quenched the reaction after 5 h that resulted in the isolation of two intermediates

Table 1. Optimazation of reaction condition for the annulation of acyl azide 1a with unactivated internal alkyne 3a[a]
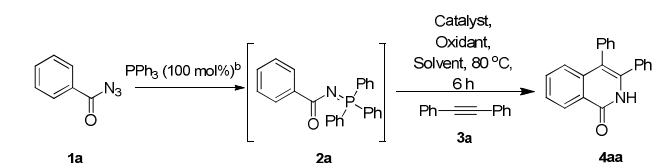
Entry	Catalyst (3.0 mol %)	Oxidant (mol %)	Solvent	Yield[d] 2a/4aa(%)
1		Cu(OAc)₂ (20)	DCE	65/-
2[c]	[RuCl₂(*p*-cymene)]₂	Cu(OAc)₂ (20)	DCE	26/32
3	[RuCl₂(*p*-cymene)]₂	Cu(OAc)₂ (20)	DCE	22/42
4	[RuCl₂(*p*-cymene)]₂	Cu(OAc)₂ (100)	DCE	-/86
5	[RuCl₂(*p*-cymene)]₂	-	DCE	78/-
6	[RuCl₂(*p*-cymene)]₂	K₂S₂O₈ (100)	DCE	63/NR
7	[RuCl₂(*p*-cymene)]₂	*t*-BuOOH (100)	DCE	65/NR
8	[RuCl₂(*p*-cymene)]₂	CuBr₂ (100)	DCE	68/NR
9	Rh(PPh₃)₃Cl	Cu(OAc)₂·(100)	DCE	55/NR
10	Pd(OAc)₂	Cu(OAc)₂·(100)	DCE	58/NR
11	Pd(OAc)₂	K₂S₂O₈ (100)	DCE	52/NR
12	Pd(OAc)₂	*t*-BuOOH (100)	DCE	38/NR
13	[RuCl₂(*p*-cymene)]₂	Cu(OAc)₂·(100)	Toluene	45/28
14	[RuCl₂(*p*-cymene)]₂	Cu(OAc)₂ (100)	THF,ACN	35/trace
15	[RuCl₂(*p*-cymene)]₂	Cu(OAc)₂ (100)	MeOH	63[e,f]
16	[RuCl₂(*p*-cymene)]₂	Cu(OAc)₂·(100)	*t*-AmOH	38[g]

Reaction conditions: [a] **1a** (1.0 equiv), **3a** (0.8 equiv), PPh₃ (1.0 equiv), [Ru(*p*-cymene)Cl₂]₂ (3.0 mol%), and Cu(OAc)₂·H₂O (100 mol %), in 5 mL DCE, 80 °C, 6 h. [b] In the absence of PPh₃ benzoyl azide underwent degradation under standard condition (with no detectable formation of **4aa**.), [c] 5.0 mol % AgSbF₆ were used. [d] Yield of isolated products. [e] Reaction stirred for 10h. [f] a yellow colored byproduct in ~10% yield. [g] byproducts: benzamide in 15% yield and a yellow colored spot in 23% yield.

iminophosphorane **2a** (32%) and benzamide (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).

Scheme 1. Treatment of presynthesized benzamide 5 with unactivated internal alkyne 3a in MeOH and DCE.
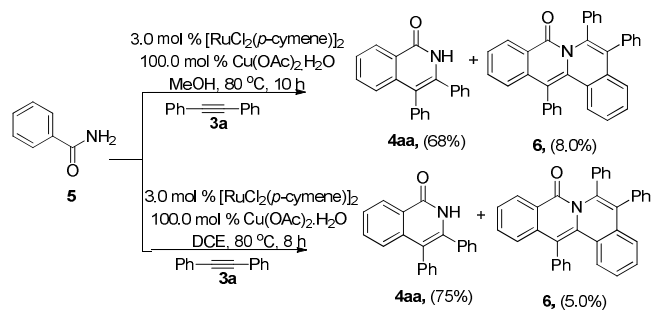
Scheme 2. Treatment of presynthesized iminophoshorane 2a with unactivated internal alkyne 3a in MeOH and DCE.
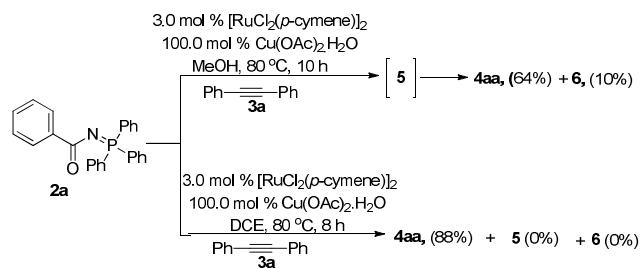

The involvement of intermediates **2a** and **5** in the transformation was further confirmed by treating presynthesized benzamide **5** (Scheme 1) and iminophosphorane **2a** (Scheme 2) separately with **3a** in MeOH/DCE. As is evident, selective transformation of **2a** to **4aa** occurred in higher 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(1H)-ones over that of benzamide **5**.

Although several literature reports[7a,8a,b] 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 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 (Scheme 1).

Table 2. Scope of the ruthenium-catalyzed C—H activation of acylazides with internal alkynes[a]
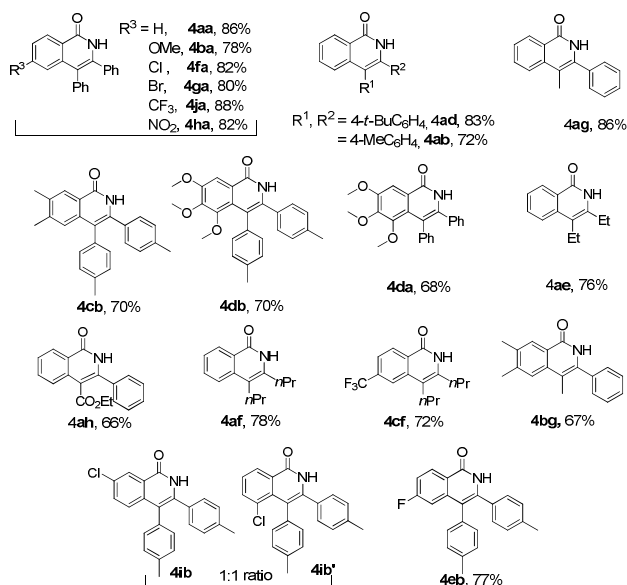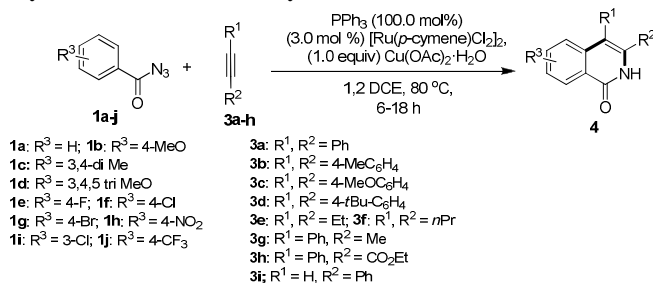
[a] Reaction condition: (1.0 equiv) of **1**, (0.8 equiv) of **3**, (100.0 mol %) of PPh$_3$, (3.0 mol %) [Ru(p-cymene)Cl$_2$]$_2$, (100 mol %) of Cu(OAc)$_2$ H$_2$O in 5 ml of DCE at 80 °C.

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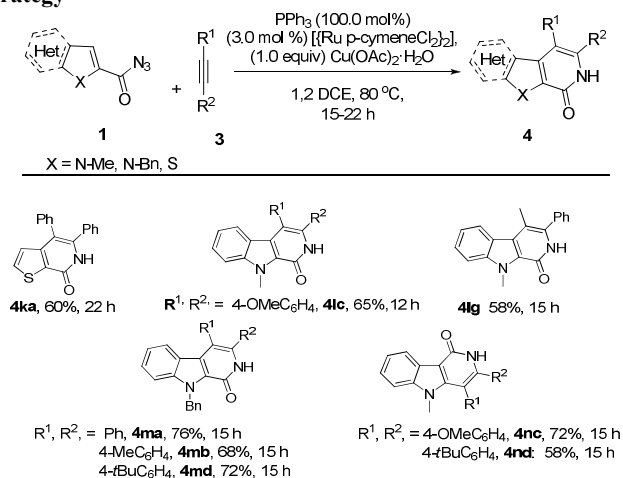

[a] Reaction condition: (1.0 equiv) of **1**, (0.8 equiv) of **3**, (100.0 mol %) of PPh$_3$, (3.0 mol %) [Ru(p-cymene)Cl$_2$]$_2$, (1.0 equiv) of Cu(OAc)$_2$.H$_2$O in 5 mL of DCE at 80 °C

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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)$_2$·H$_2$O to form an acetate-ligated species. This metal upon coordination with N-atom of the iminophosphane **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 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.
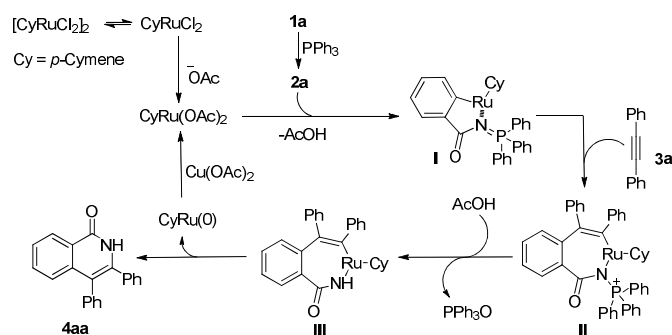
Scheme 3. A plausible mechanism for the formation of **4aa** via iminophosphorane.

In summary we have described a Ru-catalyzed *ortho* C—H activation and intramolecular C—N bond formation via in situ generated iminophosphanes 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 synhesis of heterocycles via *de novo* routes.

Notes and references

[a]Medicinal & Process Chemistry Division, CSIR-Central Drug Research Institute, B.S. 10/1, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow, 226031, India.
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[c]Sophisticated Analytical Instrumental Facility, CSIR-Central Drug Research Institute, Lucknow-226031, India.
† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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Graphical Abstract
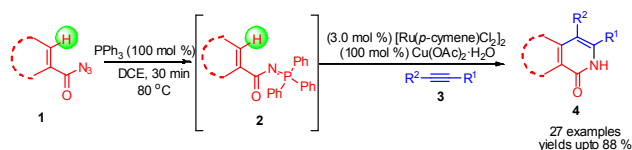
We describe ruthenium-catalyzed *ortho* C—H bond activation via in situ generation of iminophosphorane as directing group for the synthesis of annulated pyridin-2(1*H*)-ones following condensation of acyl azides with internal alkynes.

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