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Pd-catalysed synthesis of isoquinolinones and analogues *via* C–H and N–H bonds double activation†

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An atom economical synthesis of isoquinolinones and analogues *via* ligand-free Pd-catalysed C–H and N–H double activation has been developed. A series of isoquinolinones were obtained in good to excellent yields. Good regioselectivities were also observed during the activation reactions with unsymmetrical alkynes. A practical one-pot procedure for the preparation of N–H isoquinolinones is also described.

Atom economic synthesis has been one of the most popular topics and attracted great attention in the last decade.[1,2] In particular, directed C–H activation by the use of coordinative functional groups as directing handles as well as reacting sites has offered important advantages.[3]

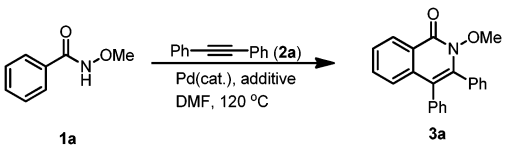
In the past two years, the construction of isoquinolinones using transition metals such as Rh and Ru has been established. Rh catalysed reactions pioneered by Guimond/Fagnou,[4] Rovis,[5] Miura[6] and Li[7] have been reported. Three types of isoquinolinones with different *N*-substituents are reported by utilizing the same $[Cp^*RhCl_2]_2$ catalyst.

While reactions using transition metal Ru have also been communicated by Ackermann[8] and Li/Wang[9] groups during our study of Pd catalysed reactions early this year, however, to the best of our knowledge, reactions using common transition metal Pd salt have not been exploited. Herein, we report the first Pd-catalysed approach for the synthesis of *N*-alkoxyl isoquinolinone *via* N–H and C–H bonds double activation of *N*-alkoxyl benzamide. By using this method, a range of isoquinolinones and derivatives are successfully achieved in good to excellent yields.

We commenced our study with the treatment of a series of benzamides with diphenyl acetylene in the presence of $Pd(OAc)_2$ as the catalyst. Benzamide, *N*-methylbenzamide and *N*-phenylbenzamide are less efficient for this transformation as only trace amounts of products were observed. Interestingly, when *N*-methoxybenzamide **1a** was treated with diphenyl acetylene, we were pleased to find that our desired isoquinolinone was formed in 27% yield (Table 1, entry 1). However, the analytical data of the isolated product did not agree with the product previously reported by Guimond/Fagnou.[4,10] Subsequently, the chemical structure of our isolated product was determined by X-ray crystallography which unambiguously confirmed the assignment of the structure of **3a** as drawn in Table 1. Reaction optimization was then carried out. Solvents such as xylenes, toluene and dichloroethane were ineffective for this transformation and the reactions only gave low yields (less than 15%), while polar solvents such as *tert*-amyl alcohol afforded no desired product even after the reaction mixture was heated at reflux for 24 hours. Gratifyingly, polar aprotic solvent, DMF led us to our desired isoquinolinone **3a** in a relatively useful 27% yield. Inspired by these results, further optimizations by the introduction of additives provided us with encouraging results and the representative results are shown in Table 1.

A range of additives were evaluated and we were pleased to find that transition metal salts $CoCl_2$ and $CuCl_2$ are good for the isoquinolinone formation as shown in Table 1 entries 2 and 3, the desired product was isolated in 42% and 31% respectively. Cheap, readily available alkaline metal salts seem to be good additives for the reaction. When NaCl was employed, the reaction yield was increased to 65% and the bromide salt gave

Table 1 Reaction conditions screening



1a 3a

Entries	Catalyst	Additive	**2a** (equiv.)	Yield
1	$Pd(OAc)_2$	—	1.5	27%
2	$Pd(OAc)_2$	$CoCl_2$	1.5	42%
3	$Pd(OAc)_2$	$CuCl_2$	1.5	31%
4	$Pd(OAc)_2$	NaCl	1.5	65%
5	$Pd(OAc)_2$	NaBr	1.5	72%
6	$Pd(OAc)_2$	$NaI{\cdot}2H_2O$	1.5	86%
7	$Pd(OAc)_2$	KI	1.5	74%
8	**$Pd(OAc)_2$**	**$NaI{\cdot}2H_2O$**	**3.0**	**93%**
9	$PdCl_2$	$NaI{\cdot}2H_2O$	3.0	47%
10	$Pd(dppf)Cl_2$	$NaI{\cdot}2H_2O$	3.0	<5%
11	$Pd(MeCN)_2Cl_2$	$NaI{\cdot}2H_2O$	3.0	25%
12	$Pd(OAc)_2$/dppf	$NaI{\cdot}2H_2O$	3.0	<5%

Reaction conditions: benzamide **1a** (45 mg, 0.3 mmol), alkyne **2a** (160 mg, 0.9 mmol), Pd catalyst (10 mol%), additive (1.0 equiv.) at 120 °C in DMF (1.5 mL, 0.2 M), 7–24 h.

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even better yield. The combination of 10% of $PdCl_2$ with 1.0 equivalent of NaOAc gave comparable results (59%) to the reaction using $Pd(OAc)_2$ and NaCl. $NaI{\cdot}2H_2O$ is proven to be the most effective additive possibly due to the soft ligand exchange processes (86% yield).[11] With the excess use of alkyne (3.0 equivalents), the reaction resulted in excellent 93% yield with the recovery of nearly 1.0 equivalent of the unreacted alkyne.

Other Pd sources were also examined, $PdCl_2$ showed a moderate reactivity and $Pd(dppf)Cl_2$ and $Pd(MeCN)_2Cl_2$ did not show better reactivities. The desired product **3a** was not formed when $Pd(dppf)Cl_2$ was used and only 25% yield was obtained when $Pd(MeCN)_2Cl_2$ was employed as the catalyst. The introduction of external ligand dppf inhibited the reactivity completely, only a trace amount of the product was obtained. It is worth noting that during the reaction, no additional oxidant is needed, air is supposed to be the green oxidant for the regeneration of active Pd(II) species.[12]

With the optimal conditions in hand, studies towards the scope of the reaction were carried out. A range of aryl carbamates were examined and a series of isoquinolinones were successfully prepared (Table 2).

For electron rich aromatic benzamides, the reactions are very successful and the corresponding isoquinolinones **3b** and **3c** were obtained in 92% and 76% yields respectively. The introduction of an electron withdrawing group seems to partially affect the reactivity as the yields of isoquinolinones **3d** and **3e** were slightly lower. Alkynes with sp^3 hybridized substituents are also efficient for isoquinolinone synthesis as products **3i** and **3o** were formed in good 66% and 62% yields.

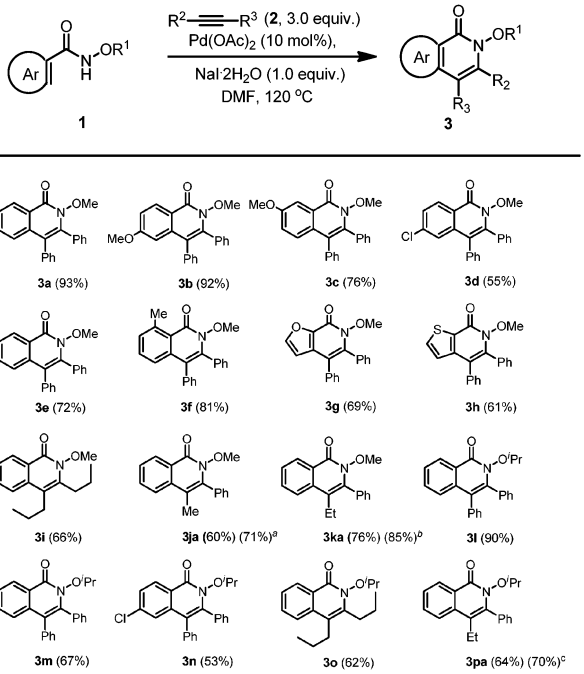
More interestingly, when furyl and thiophenyl amides were subjected to the reaction conditions, isoquinolinones **3g** and **3h** were obtained in good yields. When the unsymmetrical internal alkynes were employed, products were isolated in good yields with good regioselectivity. As shown in Table 2, isoquinolinone **3ja** and its regioisomer **3jb** were observed in a 5 : 1 ratio which can be isolated in 60% and 11% yields respectively. The regiochemistry was determined by the comparison of the corresponding known N–H isoquinolinone **4ja** (see ESI†).[4] In addition, NOE study of product **3ka** has further confirmed the regioselectivity. The regioselectivity outcome is proposed in the catalytic cycle.[13,14] These may lead to the major regioisomer with the relatively large group close to the nitrogen atom as shown in **3j** and **3k**. When *N*-isopropoxy benzamide was utilized, the reaction also demonstrated to be effective and products with electron rich and deficient substituents were successfully prepared albeit isoquinolinone **3n** was given in a moderate 53% yield. Reaction of *N*-isopropoxy benzamide and unsymmetrical alkyne behaves similar to that of the corresponding *N*-methoxy benzamide which leads to the 2 separated regioisomers in an overall 70% yield. Unfortunately, attempts on the reactions with terminal alkynes are not successful with no obvious products isolated.

In addition, the removal of the methoxy group[15] was also studied. We were pleased to find that NaH is superior to other inorganic bases[16,17] to give isoquinolinone **4a** in greater than 95% yield.

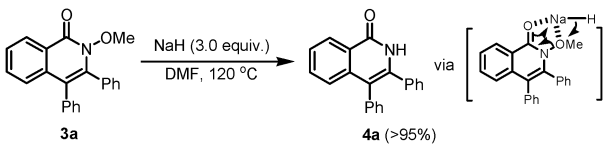
During the deprotection process, NaH is believed to be chelated by both oxygen atoms of the amide carbonyl and methoxy groups and the attack of hydride onto the oxygen atom to break the N–O bond gave the desired N–H isoquinolinone **4a** as shown in Scheme 1.

Inspired by the deprotection by NaH, a one-pot procedure was then examined. To our delight, both **1a** and **1i** were successfully transformed into the corresponding isoquinolinones after the standard C–H, N–H activation followed by the addition of NaH. As described in Scheme 2, the desired product **4a** was isolated in excellent 96% and 92% yields respectively.

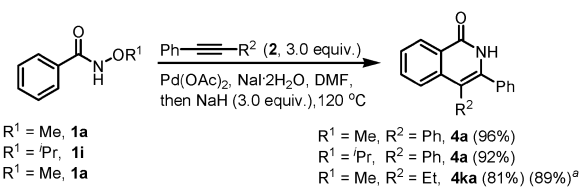
Table 2 Isoquinolinone and derivative synthesis



Standard reaction conditions: benzamide **1** (0.3 mmol), alkyne **2a** (160 mg, 0.9 mmol), $Pd(OAc)_2$ (10 mol%), $NaI{\cdot}2H_2O$ (1.0 equiv.) at 120 °C in DMF (1.5 mL, 0.2 M).[a] Separable regioisomers **3ja** and **3jb** were observed in a ratio of 5 : 1 by ^1H NMR of the crude reaction mixture and were isolated in 60% and 11% respectively. [b] In a 8 : 1 ratio with 76% and 9% isolated yields for the 2 regioisomers. [c] In a 10 : 1 ratio with 64% and 6% yields respectively.



Scheme 1 Deprotection of *N*-methoxyisoquinolinone **3a**.



[a]2 regioisomers **4ka** and **4kb** were isolated in 81% and 8% yields respectively

Scheme 2 One-pot synthesis of N–H isoquinolinones.

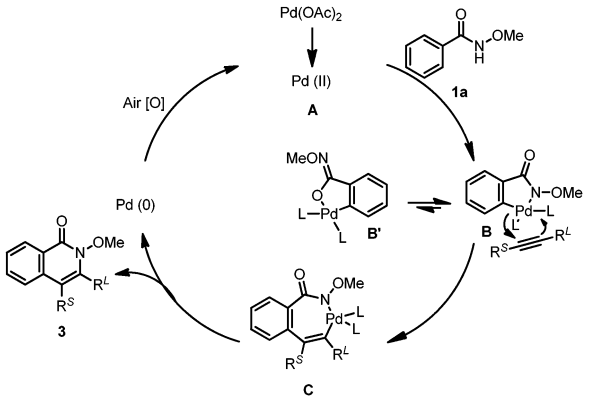


Fig. 1 Proposed catalytic cycle.

The relatively higher overall yields are due to the demethoxylated isoquinolinone ring construction. The one-pot procedure was also successfully employed for isoquinolinone **4ka** and **4kb** synthesis as shown in Scheme 2.

As previously reported in the Rh and Ru-catalysed reactions, activation of the C–H bond proceeded first and the isoquinolinone products were generated after the carbometallation and reductive elimination processes. Analogous to Rh and Ru-mediated reactions, in our case, active Pd(II) **A** was possibly formed first when $Pd(OAc)_2$ was subjected to the reaction system. Activation of the adjacent C–H bond to the amide *via* directing group participation[18] with the loss of ligands gives a 5-membered cyclic Pd adduct **B** (a similar reactive Pd intermediate had been previously characterized by Wang[19] and co-workers) which can readily undergo the thermo cycloaddition to afford the corresponding 7-membered Pd intermediate **C**.

Pd cycle **B′** may also form during the reaction which is considered to be less reactive with alkynes. The regioselectivity is due to the addition of aryl-Pd of reactive intermediate **B** onto the less hindered alkyne Csp centre which gave amide **C** in a regioselective fashion. After reductive elimination the desired product was obtained and the Pd(0) can be reoxidized by air to regenerate Pd(II) species for the next catalytic cycle (Fig. 1).

In conclusion, we have developed an efficient approach for the synthesis of isoquinolinones. A wide range of isoquinolinones were successfully constructed with moderate to good yields with good regioselectivity for unsymmetrical alkynes. In addition, we have also described a novel one-pot synthesis of N–H isoquinolinones *via* activation reaction followed by NaH dealkoxylation. The detailed mechanistic studies are currently ongoing and the communication will be reported in due course.

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Notes and references

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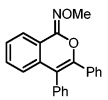
10 Under Guimond/Fagnou's reaction conditions, their proposed isoquinolinone may possibly be formed by the *O*-cyclisation and the product could possibly be 3,4-diphenyl-1*H*-isochromen-1-one *O*-methyl oxime **5a** as shown below.



5a

In their studies, *O*-cyclized product **5a** may not be easily converted into N–H isoquinolinone **4a** as described in their control reactions.

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