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Synthesis of isoindolinones *via* a ruthenium-catalyzed cyclization of *N*-substituted benzamides with allylic alcohols†

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***N*-Substituted aromatic and heteroaromatic amides reacted with substituted allylic alcohols in the presence of a ruthenium catalyst, $AgSbF_6$ and a $Cu(OAc)_2{\cdot}H_2O$ oxidant, affording 3-substituted isoindolinone derivatives with diverse substituents in good to excellent yields. A possible reaction mechanism involving a five-membered ruthenacycle intermediate was proposed and strongly supported by experimental evidence.**

The isoindolinone core unit is present in various natural products, biologically active molecules and pharmaceuticals (Fig. 1).[1] It serves as a key synthetic intermediate for synthesizing various highly useful organic molecules and natural products.[2] Particularly, the 3-substituted isoindolinone skeleton is found in various biologically active molecules.[3] As a result, various synthetic methods are available in the literature to synthesize 3-substituted isoindolinone derivatives.[4–7] Generally, 3-substituted isoindolinones are prepared by nucleophilic addition of metal reagents into isoindoline-1,3-diones,[4a] the cyclization of *ortho*-substituted aryllithiums with imines,[4b,c] or strong base-induced metalation followed by functionalization at the 3-position of isoindolinones.[4d] Additionally, 3-substituted isoindolinones can be prepared by metal-catalyzed cyclization of *ortho*-halo substituted aromatics with imines[5a] and tandem cyclization of *ortho*-halo substituted aromatics with CO and amines.[5b]

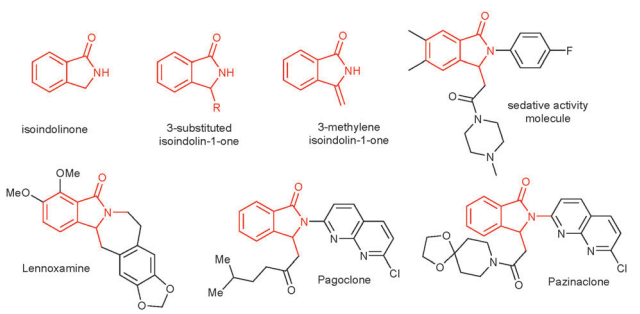

Fig. 1 Isoindolinone core biologically active molecules.

Recently, 3-substituted isoindolinones were efficiently prepared by using metal catalysts *via* C–H bond activation in a highly atom economical and environmentally friendly manner.[6–8] Aromatic imines underwent cyclization with isocyanates in the presence of a rhenium catalyst, providing 3-substituted isoindolinones.[8a] *N*-Substituted benzamides reacted with alkenes in the presence of metal catalysts, giving isoindolinones in good to excellent yields.[8b–g] In the reaction, mostly activated alkenes such as acrylates, ethyl vinyl ketone, acrylamide and conjugated 1,2-diketones were used.[8]

Due to the vast availability, easy accessibility and simple preparation of allylic alcohols, they have been widely used as alkene partners in the coupling reaction with aromatic electrophiles or organometallic reagents in the presence of metal catalysts.[9] It is important to note that in most of the catalytic reactions, allylic alcohols are chemically equivalent to α,β-unsaturated enones and aldehydes. Recently, allylic alcohols have also been efficiently used as coupling partners in the reaction with heteroatom substituted aromatics, and this transformation leads to *ortho* alkylated aromatics in the presence of metal catalysts *via* C–H bond activation.[10] Herein, we report a ruthenium-catalyzed cyclization of *N*-substituted benzamides with allylic alcohols to give 3-substituted isoindolinone derivatives in good yields. A possible reaction mechanism involving a five-membered ruthenacycle intermediate was proposed and strongly supported by experimental evidence.

Treatment of *n*-benzyl 4-methoxy benzamide (**1a**) with 3-buten-2-ol (**2a**) (2.2 equiv.) in the presence of $[\{RuCl_2(p\text{-cymene})\}_2]$ (5.0 mol%), $AgSbF_6$ (20 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (2.2 equiv.) in 1,2-dichloroethane at 110 °C for 16 h gave 3-substituted isoindolinone derivative **3aa** in 72% isolated yield (Scheme 1). Initially, the cyclization reaction was examined with various solvents such as MeOH, iso-PrOH, THF, DMF, 1,2-dimethoxyethane and toluene under similar reaction conditions. Among them, $ClCH_2CH_2Cl$ was very effective, giving **3aa** in 79% GC yield. THF, 1,4-dioxane and 1,2-dimethoxyethane were partially effective, affording product **3aa** in 34%,

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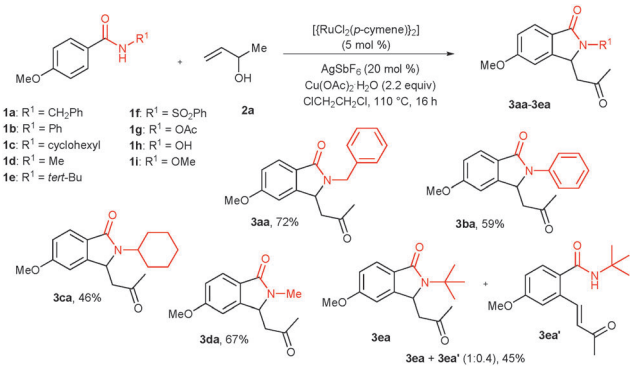


Scheme 1 Cyclization of *N*-substituted benzamides with **2a**.

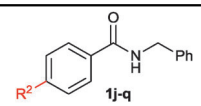
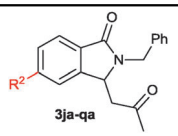
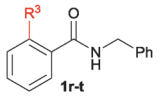
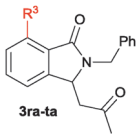
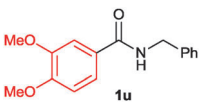
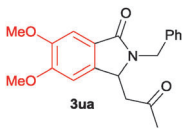
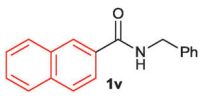
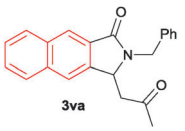
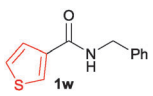
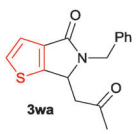
45% and 48% GC yields, whereas remaining solvents were totally ineffective.

The reaction was also tested with additives such as $AgSbF_6$, $AgBF_4$, AgOTf and KPF_6. Among them, $AgSbF_6$ was very effective, giving product **3aa** in 79% GC yield. $AgBF_4$ and AgOTf were partially effective, yielding **3aa** in 47% and 27% GC yields, respectively. KPF_6 was not suitable for the reaction. The cyclization reaction was also tested with various acetate and oxidant sources such as AgOAc, CsOAc, KOAc, NaOAc, Ag_2O and $Cu(OAc)_2{\cdot}H_2O$. Among them, $Cu(OAc)_2{\cdot}H_2O$ was very effective, providing **3aa** in 79% GC yield. Remaining acetate sources were not effective. The reaction was also tested with less than 50 mol% of $Cu(OAc)_2{\cdot}H_2O$ under an air atmosphere. However, in the reaction, product **3aa** was observed only in 38% GC yield. The reaction was tested with other catalysts (5 mol%) such as $Ru(COD)Cl_2$, $Ru(PPh_3)_3Cl_2$ and $RuCl_3{\cdot}H_2O$ apart from $[\{RuCl_2(p\text{-cymene})\}_2]$. However, no cyclization product **3aa** was observed in these complexes. The amount of the $[\{RuCl_2(p\text{-cymene})\}_2]$ catalyst (2 mol%) and (10 mol%) was also examined. Using 2 mol% and 10 mol% of the catalyst, product **3aa** was observed in 32% and 80% GC yields, respectively. Thus, 5 mol% of the catalyst amount was sufficient for the reaction. The amount of reactant **2a** (1.2 equiv. and 3.0 equiv. apart from 2.2 equiv.) was also tested. In 1.2 equiv. of **2a**, product **3aa** was observed in 55% GC yield and in 3.0 equiv. of **2a**, product **3aa** was observed in 79% GC yield. The cyclization reaction was also tested at 60 °C and 80 °C apart from 110 °C. At 60 °C, no product **3aa** was observed and at 80 °C product **3aa** was observed in 35% GC yield. Control experiments showed that in the absence of $AgSbF_6$ or $[\{RuCl_2(p\text{-cymene})\}_2]$ or $Cu(OAc)_2{\cdot}H_2O$, no **3aa** was obtained.

Under the optimized reaction conditions, the cyclization of other *N*-substituted benzamides **1b–i** with **2a** was tested (Scheme 1). *N*-Phenyl **1b** and cyclohexyl **1c** substituted benzamides reacted with **2a**, providing cyclization products **3ba** and **3ca** in 59% and 46% yields, respectively. *N*-Methyl substituted benzamide **1d** gave isoindolinone derivative **3da** in 67% yield. But, *N*-*tert* butyl benzamide **1e** provided a mixture of cyclic product **3ea** and *ortho* alkenylated product **3ea′** in 45% combined yield and in a 1 : 0.4 ratio. In other *N*-substituted benzamides **1f–i**, the expected cyclization product was not observed.

The scope of the cyclization reaction was examined using *N*-benzyl substituted benzamides **1j–v** (Table 1). Benzamides **1j** and **1k** reacted efficiently with **2a**, providing the cyclization products **3ja** and **3ka** in 69% and 60% yields, respectively (entries 1 and 2).

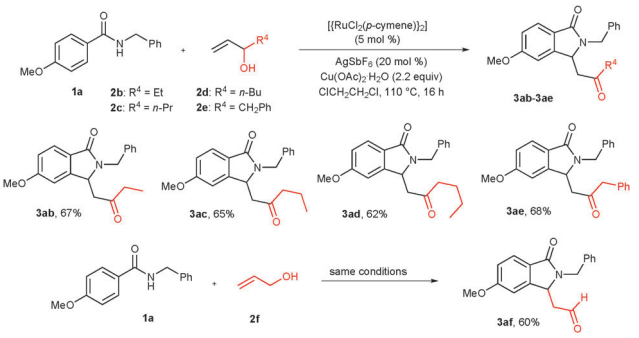
Table 1 Scope of the *N*-benzyl substituted benzamides[a]

Entry	1	Product 3	Yield[b] (%)
			
	1j-q	3ja-qa	
1	**1j**: R^2 = Me	**3ja**: R^2 = Me	69
2	**1k**: R^2 = H	**3ka**: R^2 = H	60
3	**1l**: R^2 = I	**3la**: R^2 = I	61
4	**1m**: R^2 = Br	**3ma**: R^2 = Br	59
5	**1n**: R^2 = Cl	**3na**: R^2 = Cl	58
6	**1o**: R^2 = F	**3oa**: R^2 = F	47
7	**1p**: R^2 = CF_3	**3pa**: R^2 = CF_3	54
8	**1q**: R^2 = NO_2	**3qa**: R^2 = NO_2	46
			
	1r-t	3ra-ta	
9	**1r**: R^3 = OMe	**3ra**: R^3 = OMe	80
10	**1s**: R^3 = Me	**3sa**: R^3 = Me	65
11	**1t**: R^3 = Br	**3ta**: R^3 = Br	62
12	 1u	 3ua	53
13[c]	 1v	 3va	58
14	 1w	 3wa	60[c]

[a] All reactions were carried out using **1j–w** (100 mg), ethyl-2-buten-2-ol (**2a**) (2.2 equiv.), $[\{RuCl_2(p\text{-cymene})\}_2]$ (5 mol%), $AgSbF_6$ (20 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (2.2 equiv.) in $ClCH_2CH_2Cl$ (3.0 mL) at 110 °C for 16 h. [b] Isolated yield. [c] The reaction was carried at 110 °C for 28 h.

Halogen groups such as I, Br, Cl and F substituted benzamides **1l–o** reacted efficiently with **2a**, affording products **3la–3oa** in good to moderate yields, respectively (entries 3–6). Interestingly, electron-withdrawing groups such as CF_3 and NO_2 substituted benzamides **1p** and **1q** reacted with **2a**, giving cyclization products **3pa** and **3qa** in 54% and 46% yields, respectively (entries 7 and 8). Apart from the *para* substituted benzamides, *ortho* OMe, Me and Br substituted benzamides **1r–t** also efficiently participated in the reaction, yielding products **3ra–ta** in 80%, 65% and 62% yields, respectively (entries 9–11). Unsymmetrical 3,4-dimethoxy (**1u**) and 2-naphthyl (**1v**) substituted benzamides regioselectively reacted with **2a** yielding products **3ua** and **3va** in 53% and 58% yields, respectively (entries 12 and 13). In substrates **1u** and **1v**, the C–H bond activation takes place at the C-6 position of the benzene ring and at the C-3 position of the naphthalene ring selectively. Interestingly, heteroaromatic amide **1w** also efficiently participated in the reaction, affording product **3wa** in 60% yield (entry 14).

The scope of the cyclization reaction was also further examined using substituted allylic alcohols (Scheme 2). Treatment of

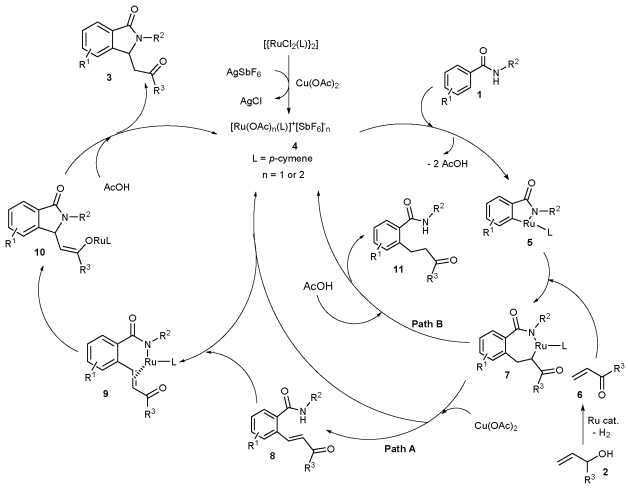


Scheme 2 Scope of the substituted allylic alcohols.

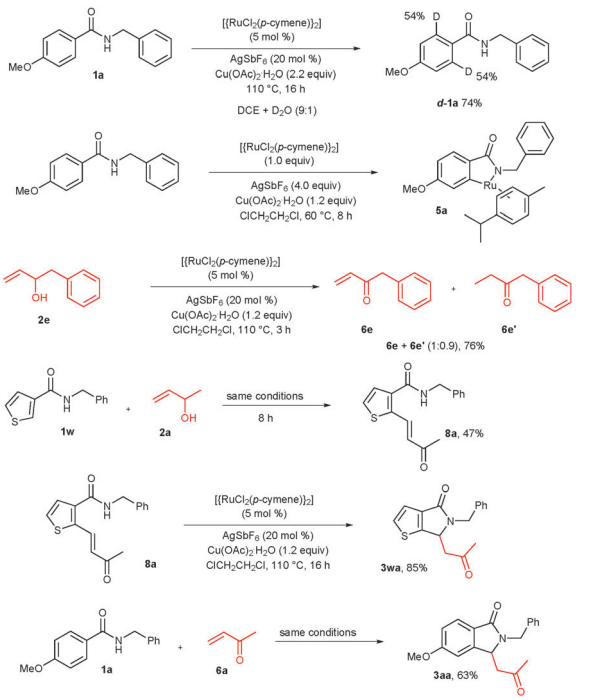
pent-1-en-3-ol (**2b**), hex-1-en-3-ol (**2c**) and hept-1-en-3-ol (**2d**) with benzamide **1a** under similar reaction conditions gave cyclization products **3ab–ad** in 67%, 65% and 62% yields, respectively. 1-Phenylbut-3-en-2-ol (**2e**) also nicely participated in the reaction, affording the corresponding cyclization product **3ae** in 68% yield. Interestingly, prop-2-en-1-ol (**2f**) reacted efficiently with **1a**, giving a formyl substituted cyclic compound **3af** in 60% yield.

Based on the previous reports[6–10] and our observation, a possible reaction mechanism is proposed in Scheme 3. Basically, a multi-step reaction is involved in the cyclization reaction. First, $AgSbF_6$ likely removes the Cl^- ligand from the $[\{RuCl_2(p\text{-cymene})\}_2]$ complex in the presence of $Cu(OAc)_2$ providing a cationic ruthenium acetate species **4**. Coordination of the nitrogen atom of **1** to the ruthenium species **4** followed by *ortho*-metalation provides ruthenacycle intermediate **5**. Coordinative insertion of α,β-unsaturated enone **6** into the Ru–carbon bond of intermediate **5** gives intermediate **7**. We strongly believe that the allylic alcohols **2** convert into α,β-unsaturated enones **6** in the presence of the ruthenium catalyst and $Cu(OAc)_2$.[11] β-Deprotonation of intermediate **7** by an acetate source followed by protonation of nitrogen affords *ortho*-alkenylated benzamide **8** and regenerates the ruthenium species **4** (proceeds *via* **path A**).[11c] Later, coordination of the nitrogen atom of *ortho*-alkenylated benzamide **8** into ruthenium species **4** followed by intramolecular coordination of the double bond into ruthenium affords intermediate **9** and AcOH. Intramolecular coordinative insertion of the N–Ru bond of intermediate **9** into the alkene moiety followed by enolization provides ruthenium enolate intermediate **10**. Protonation of intermediate **10** in the presence of AcOH provides product **3** and regenerates the active ruthenium species **4**. The control of the formation of product **11** which proceeds *via* enolization of intermediate **7** followed by protonation is highly important to successfully carry out the present cyclization reaction (*via* **path B**).[10]

The formation of a key five-membered ruthenacycle intermediate **5** is the rate determining reversible step in the reaction. To support the reversible step, *N*-benzyl 4-methoxy benzamide (**1a**) was treated with a ruthenium catalyst, $AgSbF_6$ and $Cu(OAc)_2{\cdot}H_2O$, D_2O in DCE solvent at 110 °C for 16 h. As expected, 54% deuterium incorporations were observed at both *ortho* carbons of benzamide ***d*-1a** in a combined 74% yield (Scheme 4). In the meantime, we have tried to isolate the key ruthenacycle intermediate **5** in the reaction of 4-methoxy benzamide **1a** with a stoichiometric amount of the ruthenium complex (1.0 equiv.), $AgSbF_6$ (4.0 equiv.) and $Cu(OAc)_2{\cdot}H_2O$ (1.2 equiv.) in DCE solvent at 60 °C for 8 h. In the reaction,

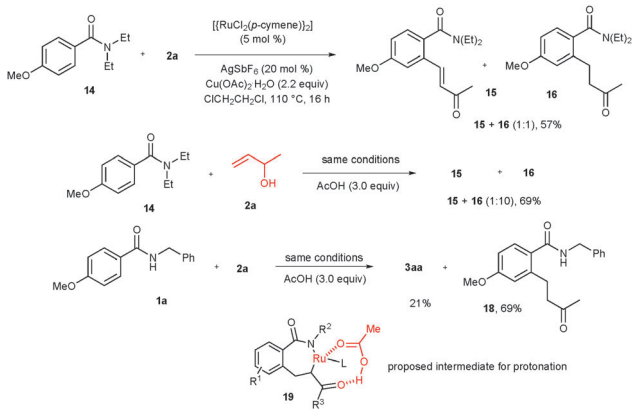


Scheme 3 Proposed mechanism.



Scheme 4 Mechanistic evidence.

metalacycle intermediate **5** was isolated. However, we were not able to crystallize intermediate **5**. But, the complex **5** was tentatively assigned by ^1H, ^{13}C NMR, HRMS and MALDI-TOF spectroscopic techniques (see ESI†). To confirm the formation of activated alkene **6**, 1-phenylbut-3-en-2-ol (**2e**) was treated with the ruthenium catalyst, $AgSbF_6$ and $Cu(OAc)_2{\cdot}H_2O$ at 110 °C for 3 h. In the reaction, approximately a 1 : 1 mixture of 1-phenylbut-3-en-2-one (**6e**) and the reduced 1-phenylbutan-2-one (**6e′**) were observed in a combined 76% yield. It seems that in the cyclization reaction, initially product **6e** is formed which further reacts with benzamide **1** providing the cyclization product **3**. If benzamide is not present in the reaction mixture, the alkene moiety of **6e** is subsequently reduced. Further, we have tried to isolate *ortho* alkenylated benzamide **8** in the reaction



Scheme 5 Reaction of *N*,*N*-diethyl benzamide with **2a**.

of 2-thienyl amide (**1w**) with **2a** under the optimized reaction conditions at the shorter reaction time of 8 h. In the reaction, the expected alkenylated product **8a** was observed in 47% yield. Later, *ortho* alkylated benzamide **8a** was treated with the ruthenium catalyst, $AgSbF_6$ and $Cu(OAc)_2{\cdot}H_2O$ at 110 °C for 16 h giving the expected cyclic compound **3wa** in 85% yield. Further, benzamide **1a** reacted with methyl vinyl ketone (**6a**) under the optimized reaction conditions providing the expected cyclic product **3aa** in 63% yield. This experimental evidence clearly supports the proposed mechanism in Scheme 3.

To successfully carry out the present cyclization reaction, suppression of the enolization of intermediate **7** into **11** is highly important. It is known that *N*,*N*-disubstituted benzamides react with allylic alcohols leading to *ortho* alkylated benzamides in the presence of rhodium or ruthenium complexes.[10] But, in the present reaction, *N*-substituted benzamides reacted with allylic alcohols yielding isoindolinone derivatives **3**. To know the clear mechanism, we have tried the reaction of *N*,*N*-diethyl benzamide **14** with **2a** under the optimized reaction conditions (Scheme 5). In the reaction, *ortho* alkenylated benzamide **15** and *ortho* alkylated benzamide **16** were observed in combined 57% yields in a 1 : 1 ratio. But, in the presence of AcOH (3.0 equiv.) under similar reaction conditions, the same reaction provided a major amount of *ortho* alkylated benzamide **16** along with a minor amount of **15** in 69% yield in a 10 : 1 ratio. Similarly, the reaction of *N*-substituted benzamide **1a** with **2a** was tried in the presence of 3.0 equiv. of AcOH under the optimized reaction conditions. In the reaction, cyclization product **3aa** and *ortho* alkylated benzamide **18** were observed in 21% and 69% yields, respectively. At this stage, we conclude that an excess amount of AcOH might increase the electrophilicity of the carbonyl group in intermediate **7** *via* protonation. It is likely that intermediate **19** could be formed. Thus, instead of β-hydride elimination, enolization takes place effectively.[10c,12]

In conclusion, we have demonstrated a ruthenium-catalyzed cyclization of *N*-substituted benzamides with allylic alcohols in the presence of a ruthenium catalyst. A possible reaction mechanism involving a five-membered ruthenacycle intermediate was proposed and strongly supported by experimental evidence.

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