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Microwave-Assisted Ruthenium-Catalysed *ortho*-C–H Functionalization of *N*-Benzoyl α-Amino Ester Derivatives

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Abstract: A microwave-assisted highly efficient intermolecular C–H functionalization sequence has been developed to access substituted isoquinolones using α-amino acid esters as a directing group. This methodology enables a wide range of *N*-benzoyl α-amino ester derivatives to react *via* a Ru-catalysed C–H bond activation sequence, to form isoquinolones with moderate to excellent yields. As an additional advantage, our strategy proved to be widely applicable and also enabled the reaction of alkenes to provide access to alkenylated benzamides. The methodology was also extended towards the synthesis of isoquinoline alkaloids derivatives *viz.* oxyavicine and a dipeptide. The developed protocol is simple and cheap, avoids tedious workup procedures and works efficiently under MW irradiation.

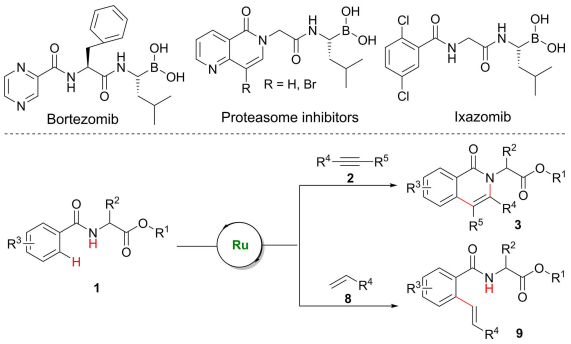
Keywords: Microwave; C–H activation; *N*-benzoyl α-amino ester; ruthenium; alkynes; isoquinolones

1. Introduction

Isoquinolones are one of the important classes of nitrogen-containing compounds. This core is present in various natural products and biologically active molecules.[1] In addition, isoquinolones are also employed as intermediates for the synthesis of other heterocycles such as indenoisoquinolines, protoberberines, and dibenzoquinolizines,[2] and are undeniably prominent in medicinal chemistry.[3] Accordingly, there is a continued strong demand for a step-economical and environmentally benign syntheses of this heterocyclic scaffold. In the last decades, multiple strategies have been developed for the synthesis of this priviledged scaffold,[4] with transition-metal catalysed C–H bond activation[5] taking the front lead recently.[6] To overcome the key obstacles of achieving site selectivity in the intermolecular C–H bond functionalization, directing group assistance has already been proven to be a powerful strategy.[7] In this respect, Rh(III), Pd(II), Ni(II) or low cost Ru(II) complexes have been widely used for the promotion of oxidative coupling between internal alkynes and amides, to yield the corresponding isoquinolones.[8]

Readily available natural α-amino acids are one of nature's most attractive and versatile building blocks for the synthesis of natural products and bio-molecules,[9] and are used for the generation of different complex organic compounds[10] In addition, several reports are available where the presence of amino acid modification is known to enhance the bioavailability as well as the biological activity of the molecules (Scheme 1).[11] Therefore, direct C–H functionalization of amino acid derivatives is an important pursuit for organic chemist as can be seen from recent examples.[12] In 2014, Chatani and co-workers reported one of the few examples, using *N*-benzoyl α-amino ester derivatives for the synthesis of bi(hetero)aryl compounds through palladium catalysis.[13] In spite of this, the use of readily available amino acids as nitrogen source for the building of a heterocycle is seldom reported employing C–H functionalization.

Thus, in continuation of our studies on the use of amino acid esters as a natural nitrogen source[14] we thought to use the CONH(R) group of *N*-benzoyl α-amino esters as directing group to build up the isoquinolone scaffold **3** through Ru-catalyzed C–H bond annulation of alkynes **2**, where the amino ester



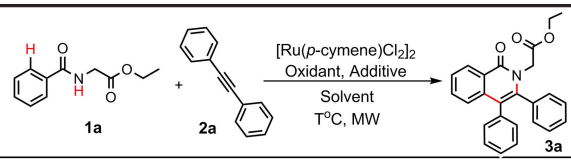
Scheme 1. Ruthenium-catalysed C–H activation of α-amino acid esters and its biological significance.

arm plays not only the role of a coordinating group, but also functions as a region for further modifications. Notably, our strategy proved to be widely applicable and also enabled annulation of alkenes **8** to provide access to alkenylated benzamides **9** (Scheme 1). As additional advantages, the developed protocol is simple and cheap, avoids inert conditions, tedious workup procedures and works efficiently under microwave irradiation. Since the past decade, researchers are exploring microwave-assisted C–H activation approaches to develop clean and efficient access towards the construction of various heterocyclic scaffolds.[15]

2. Results and Discussion

For the rapid and efficient synthesis of isoquinolones, we initiated our investigations by exploring the intermolecular cyclization of *N*-benzoyl glycine ester **1a** with diphenylacetylene **2a** using a cationic Ru(II) system in the presence of $Cu(OAc)_2$ as oxidant in various solvents at 120°C under microwave irradiation (Table 1, entries 1-5). Among all, *t*-AmOH proved to be the best choice, affording the annulation product **3a** in 49% yield (Table 1, entry 1). No improvement in product yield was achieved using co-catalytic amounts of other silver additives (Table 1, entries 6–8). Increasing the amount of either the additive (from 10 to 20 mol%) or the oxidant (from 0.5 to 1 mmol) resulted in significant decrease in yields of the desired product (32 and 36%, respectively, entries 9 and 10). The yield of the isolated product was surprisingly increased to 66% by performing the reaction without any additive indicating that the cationic Ru(II)-system is not needed for the reaction (entry 11). Follow-up reactions revealed that replacing $Cu(OAc)_2$ with other oxidants provided lesser product yields (entries 12, 13). Also, running the reaction at lower or higher temperature did not result in the ameliorated conditions (entries 14, 15). Further optimization focused on the amount of oxidant (entry 16), the reactants (entries 17–19) and catalyst (entry 20) which reveals that the use of 2 equivalents of amino acid ester and 10 mol% of catalyst led to a strong increase in yield of the desired product **3a**, up to 92%. The structure of **3a** was confirmed by ^1H and ^{13}C NMR analysis and mass spectrometry. To know the effect of microwave irradiation, the reaction was performed under conventional heating which resulted in 72% yield over 24 h (entry 21) in comparison to 92% yield obtained under microwave irradiation after 1 h (entry 20).

Table 1. Optimization of the reaction conditions.[a]

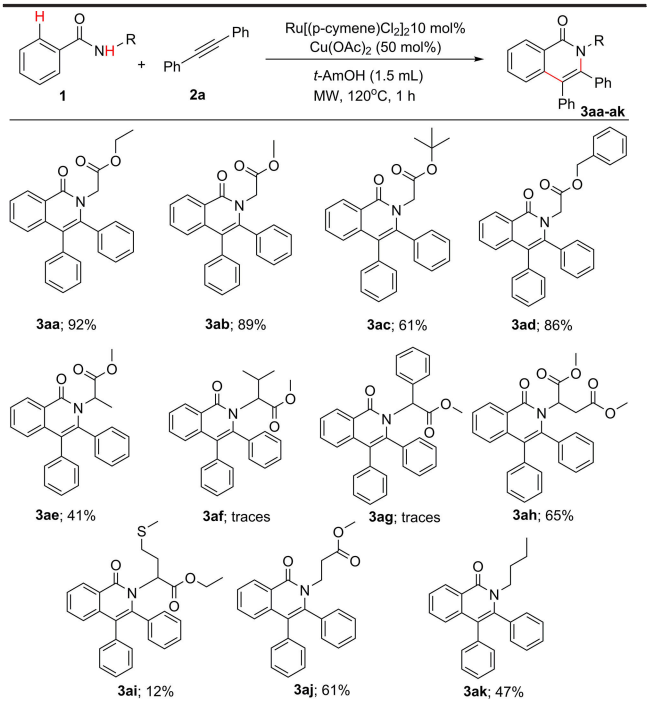


Entry	Oxidant	Solvent	Additive	T [°C]	Yield [%][b]
1	$Cu(OAc)_2$	*t*-AmOH	$AgSbF_6$	120	49
2	$Cu(OAc)_2$	H_2O	$AgSbF_6$	120	nd
3	$Cu(OAc)_2$	IPA	$AgSbF_6$	120	41
4	$Cu(OAc)_2$	MeOH	$AgSbF_6$	120	27
5	$Cu(OAc)_2$	DCE	$AgSbF_6$	120	12
6	$Cu(OAc)_2$	*t*-AmOH	AgOTf	120	42
7	$Cu(OAc)_2$	*t*-AmOH	$AgNTf_2$	120	48
8	$Cu(OAc)_2$	*t*-AmOH	$AgBF_4$	120	45
9[c]	$Cu(OAc)_2$	*t*-AmOH	$AgSbF_6$	120	32
10[d]	$Cu(OAc)_2$	*t*-AmOH	$AgSbF_6$	120	36
11	$Cu(OAc)_2$	*t*-AmOH	-	120	66
12	$Cu(OAc)_2.H_2O$	*t*-AmOH	-	120	40
13	Ag_2CO_3	*t*-AmOH	-	120	35
14	$Cu(OAc)_2$	*t*-AmOH	-	110	53
15	$Cu(OAc)_2$	*t*-AmOH	-	130	39
16[d]	$Cu(OAc)_2$	*t*-AmOH	-	120	65
17[e]	$Cu(OAc)_2$	*t*-AmOH	-	120	58
18[f]	$Cu(OAc)_2$	*t*-AmOH	-	120	72
19[g]	$Cu(OAc)_2$	*t*-AmOH	-	120	81
20[g,h]	**$Cu(OAc)_2$**	***t*-AmOH**	**-**	**120**	**92**
21[g,h,i]	$Cu(OAc)_2$	*t*-AmOH	-	120	72

[a] Unless otherwise stated, all reactions were run with **1a** (0.1 mmol), **2a** (0.1 mmol), Ru-catalyst (5 mol%), additive (10 mol%), oxidant (50 mol%) in the indicated solvent (1.5 mL) at 120 °C for 1 h under MW irradiation using a maximum power of 100 W.
[b] Isolated yields.
[c] 20 mol% additive was used.
[d] 1 equiv. Oxidant was used.
[e] 1.5 equiv. of **2a** was used.
[f] 1.5 equiv. of **1a** was used.
[g] 2 equiv. of **1a** was used;
[h] 10 mol% of Ru-catalyst was used.
[i] Conventional heating for 24 h, nd = not detected.

With the optimized reaction conditions in hand (Table 1, entry 20), we evaluated the scope of the methodology. Initially, the influence of the α-amino ester moiety on the reaction was studied (Table 2).

Table 2. Influence of the amino acid ester moiety.[a]



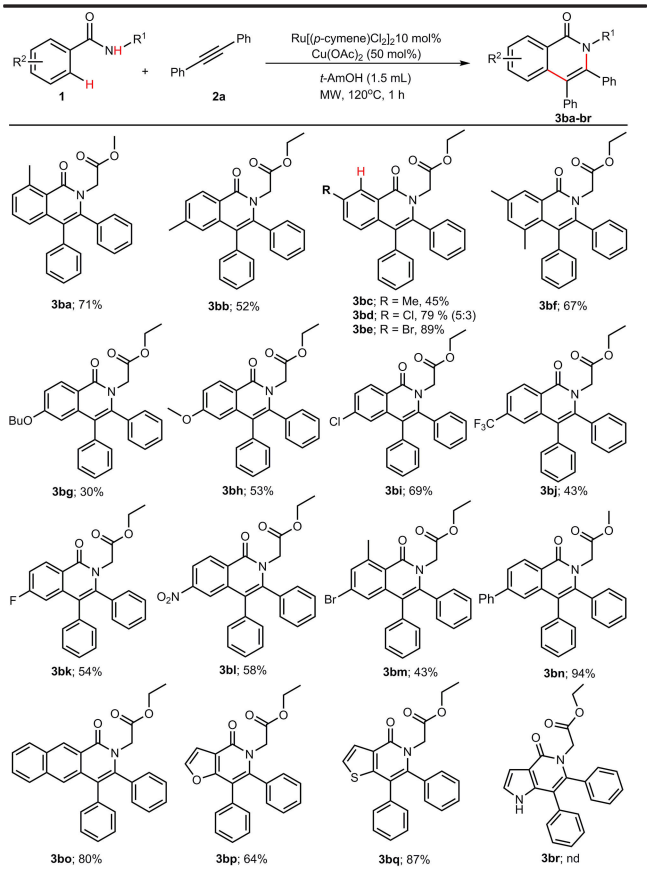
[a] Isolated yields, under optimized conditions as described in Table 1.

Switching from an ethyl ester (**3aa**) to a methyl ester **3ab**) or benzyl ester (**3ad)** has only a small negative effect on the reaction yield, while replacement by a *t*-Bu ester (**3ac**) resulted in significant decrease.

On the other hand, when a tertiary α-carbon amino ester was introduced on the substrate, the yield decreased drastically as a result of the steric hindrance (**3ae**–**3ag**). However, when the α-substituent was a CH_2CO_2Me group (**3ah**), the yield was 65%. A very low yield was obtained with sulphur containing CH_2CH_2SMe group (**3ai**). To emphasize the role of the ester as a directing group, the β-amino ester compound **3aj** was reacted under the same conditions, resulting in a moderate yield of 61% while in case of *N*-butyl amide **3ak**, only 47% yield was obtained. This is probably due to stabilization of the intermediates by the ester group through weak coordination to the metal centre.[8] In addition, no reaction was observed with replacing free NH-amide group with N-methyl amide.

Next, the reaction scope was evaluated with respect to a series of aromatic acids (Table 3), all giving the corresponding products in moderate to good yields. The catalytic system proved to be broadly applicable and *ortho*- (**3ba**), *para*- (**3bb**), *meta*- (**3bc**–**3be**) and di-substituted (**3bf**) substrates were efficiently converted into the corresponding isoquinolones. Notably, the *meta*-substituted amide mainly afforded the less hindered regioisomer (**3bc**–**3be**). Further the reaction was successful for both electron-rich and electron-poor functional groups (**3bg**–**3bm**). However, it turned out that amide derived from *p*-butoxy acid (**3bg**) gave relatively lower yield. Also, the substrate derived from biphenyl carboxylic acid (**3bn**) reacted smoothly furnishing 94% yield under the optimized conditions. We were also pleased to observe that naphthyl and heteroaromatic substrates, such as furan and thiophene (**3bo**–**3bq**) proved suitable for the alkyne annulation process with the β-naphthyl derivative affording isoquinolone **3bo** as sole product (Table 3). However, the reaction was found incompatible with nitrogen heterocycles such as pyrrole (**3br**).

Table 3. Influence of the (hetero)aromatic acid moiety.[a]

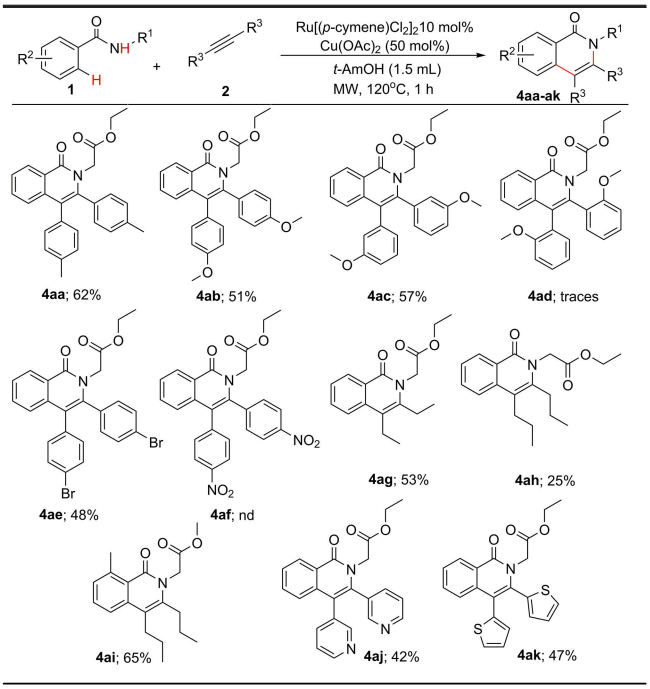


[a] Isolated yields, under optimized conditions as described in Table 1.

Next, the influence of the alkyne subunit on the reaction outcome was examined (Table 4). The reaction proceeded smoothly with symmetrical aryl-, or alkyl-substituted internal alkynes, such as *p*-methyl- (**4aa**), *p*- or *m*-methoxy- (**4ab**, **4ac**), *p*-bromo- (**4ae**) substituted diphenylacetylenes or 3-hexyne (**4ag**) and 4-octyne (**4ah**, **4ai**), providing the corresponding

products in moderate to good yields. Further, the reaction was found sensitive to steric hindrance around the alkyne moiety as only traces of product are obtained in case of *o*-methoxy substituted diphenylacetylene (**4ad**). Also, alkyne bearing strong electron withdrawing nitro- group (**4af**) did not react under the optimized conditions. Further the reaction was found compatible with heteroaromatic alkynes (**4aj**, **4ak**).

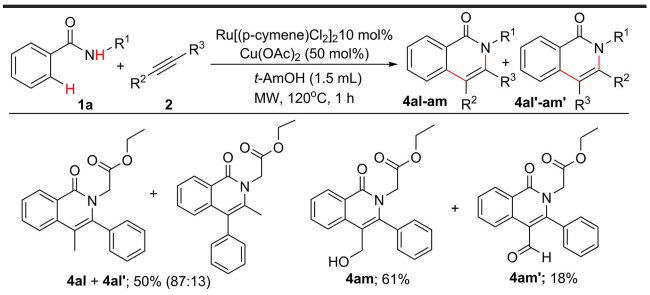
Table 4. Influence of the symmetrical alkyne moiety.[a]



[a] Isolated yields, under optimized conditions as described in Table 1.

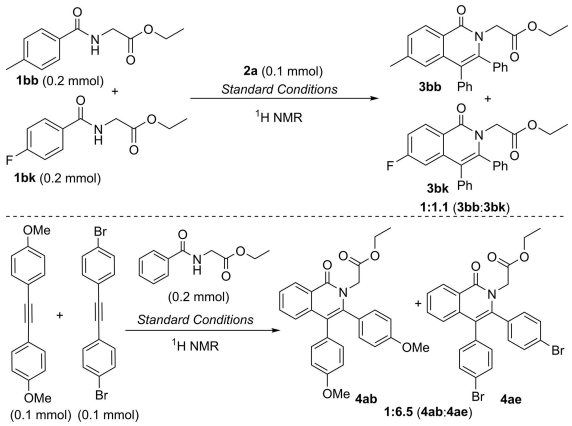
When unsymmetrical alkynes were employed (Table 5), mainly a single regioisomer is observed. The use of methyl-phenyl disubstituted alkyne gave 50% yield with moderate regioselectivity with the phenyl group installed at the 3-position of the heterocycle (**4al**) which substantiates with the previous reports.[8] With alkynes such as 3-phenyl-2-propyn-1-ol, reaction went smoothly to deliver the desired product **4am** along with the formation of oxidised product **4am′** in 18% yield. Unfortunately, under the current reaction conditions, terminal alkynes failed to afford the corresponding cycloadducts.

Table 5. Influence of the unsymmetrical alkyne moiety.[a]



[a] Isolated yields, under optimized conditions as described in Table 1.

To determine whether or not the electronic nature of the substrates has an influence on the catalytic C–C coupling reaction, equimolar amount of compound **1bb** and **1bk** were reacted under the same conditions with 0.1 mmol of diphenylacetylene **2a**. Both *N*-benzoyl glycine esters afforded almost the same yield (1:1.1), which suggests that the electronic properties of the *N*-benzoyl glycine esters has little effect on the catalytic reaction. Similarly, intermolecular competition experiments with differently substituted alkynes (OMe *vs* Br) showed that electron-deficient ones reacts preferentially (Scheme 2).

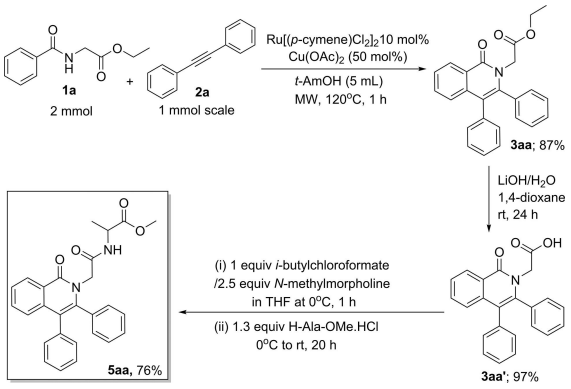


Scheme 2. Intermolecular competition experiments.

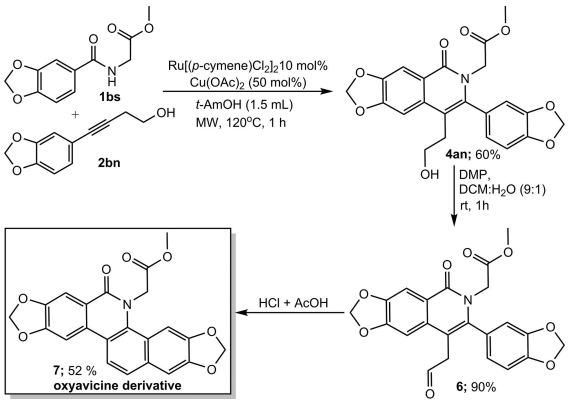
To determine whether or not the electronic nature of the io-doarene has an effect on the catalytic C–C coupling reaction, compound **1a** was reacted under the same conditions with 1.5 equivalents of 4-iodoanisole and 4-iodobenzotrifluoride under the opti mized conditions. Both iodoarenes afforded almost the same yield, which suggests that the electronic properties of the iodoarene has little affect on the catalytic reaction (Scheme 1).

To evaluate the potential of the catalytic system and to expand the scope of this reaction, **1a** and **2a** were reacted on a 1 mmol scale to give isoquinolone **3aa** in 87% yield (Scheme 3). Compound **3aa** can be easily hydrolysed into the respective acid **3aa′** in 97% yield. Thereafter, by classical organic chemistry, another amino acid can be attached to give the aryl peptide **5aa**. In addition, the successful synthesis of **4am** prompted us to synthesize a derivative of oxy-

avicine alkaloid **7** (Scheme 4), which is known to exhibit analgesic and anti-inflammatory activities, besides its use in treatment of ophthalmic disorders.[16] Moreover, this methodology could also be used for the synthesis of benzo[*c*]phenanthridine alkaloids such as oxynitidine and oxysanguinarine. Compound **4an** as obtained from our developed methodology is then converted to the corresponding aldehyde *via* Dess-Martin periodinane (DMP) oxidation. After a successful acid-catalysed ring-closing and dehydration reaction, the oxyavicine derivative was obtained in 52% yield.



Scheme 3. Extension of scope towards a dipeptide.

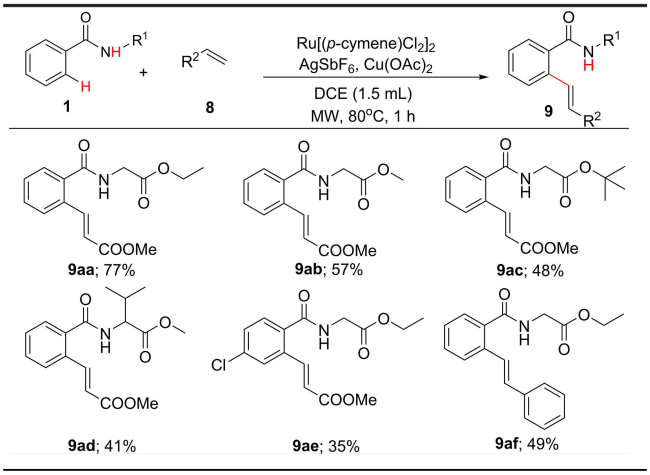


Scheme 4. Extension of the scope towards an oxyavicine derivative.

In addition to triple bonds, we successfully applied the developed process to alkenes as coupling partners after a small optimization (see SI, Table 2), resulting in the formation of alkenylated benzamides **9aa–9af** in moderate to good yields. Addition of a catalytic amount of $AgSbF_6$ was helpful for the transformation in DCE as reaction solvent (Table 6).

Thus, based on the above results, preliminary mechanistic studies (see SI, Scheme S1) and previous reports,[8] a plausible mechanism is presented in

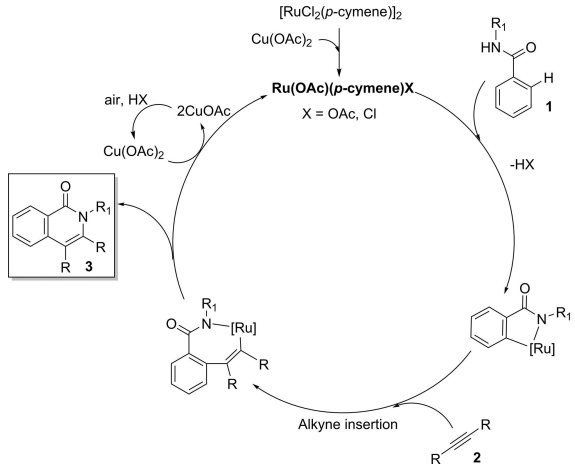
Table 6. Scope of alkenes.[a]



[a] Unless otherwise stated, all reactions were run with **1** (0.1 mmol), **8** (0.12 mmol), Ru-catalyst (5 mol%), additive (10 mo%), oxidant (25 mol%) in DCE (1.5 mL) at 80 °C for 1 h under MW irradiation using a maximum power of 200 W.

[b] Isolated yields.

Scheme 5. First, $[RuCl_2(p\text{-cymene})]_2$ undergoes ligand exchange with $Cu(OAc)_2$ to give the active catalytic species, which coordinates to the nitrogen atom of the *N*-benzoyl glycine ester moiety *via* NH deprotonation. This is followed by C–H activation through elimination of AcOH, forming the five membered ruthenacycle. Further coordination of alkyne **2**, followed by insertion and reductive elimination afforded the final product **3**. The active catalyst species is then regenerated by $Cu(OAc)_2$ and air for the next catalytic cycle (Scheme 5).



Scheme 5. Proposed mechanistic pathway.

3. Conclusion

In summary, we have devloped a microwave-assisted highly efficient intermolecular C–H functionalization sequence to access substituted isoquinolones with α-amino acid esters as directing group. This methodology enables a wide range of *N*-benzoyl α-amino ester derivatives to react *via* a Ru-catalysed C–H bond activation sequence to form isoquinolones with moderate to excellent yields. Based on the experimental results and spectroscopic analyses, we propose that the NH-amido and carbonyl ester groups both play a major role in the catalytic reaction. As an additional advantages, our strategy proved to be widely applicable and also enabled participation of alkenes to provide access to alkenylated benzamides. The methodology was also extended towards the synthesis of isoquinoline alkaloid derivatives *viz*. Oxyavicine and a dipeptide. This family of isoquinolone compounds bearing an amino acid ester side chain represent potential bioactive molecules for further studies.The developed protocol is simple and cheap, avoids inert conditions, tedious workup procedures and works efficiently under MW irradiation.

Experimental Section

Representative procedure for ruthenium-catalyzed oxidative annulation. Synthesis of **3a** (Table 1, entry 12): A mixture of **1a** (67.5 mg, 0.50 mmol), **2a** (178 mg, 1.00 mmol), [{$RuCl_2$(*p*-cymene)}2] (15.3 mg, 5.0 mol%), and $Cu(OAc)_2{\cdot}H_2O$ (200 mg, 1.00 mmol) in tAmOH (2.0 mL) was stirred at 100 °C under nitrogen for 22 h. After cooling the reaction mixture to ambient temperature, it was diluted with aq NH_3 (75 mL, 1.0 wt%) and extracted with EtOAc (3■75 mL). The combined organic phase was washed with brine (50 mL) and dried over Na_2SO_4. After filtration and evaporation of the solvents in vacuum, the crude product was purified by column chromatography on silica gel (n-hexane/EtOAc: 4:1) to yield **3a** as a colorless solid (118 mg, 76%).

Representative procedure for ruthenium-catalyzed oxidative annulation. To an oven-dried 10 mL microwave vial equipped with a magnetic stirring bar, ethyl 2-benzamidoacetate **1a** (41.4 mg, 0.2 mmol), diphenylacetylene **2a** (17.8 mg, 0.1 mmol), [Ru(*p*-cymene)Cl_2] (6.12 mg, 0.01 mmol), copper(II) acetate (9.08 mg, 0.05 mmol) and 2-methyl-2-butanol (1.5 mL) were added under atmospheric air. The mixture was heated under microwave-irradiation for 60 min at 120 °C using a maximum power of 200 W followed by cooling. The mixture was filtered through a celite pad and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (eluent: *n*-heptane/EtOAc) to afford the desired product whose structure was further confirmed by ^1H, ^{13}C-NMR and HR-MS.

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