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# Ruthenium-catalyzed C–H/O–H and C–H/N–H bond functionalizations: oxidative annulations of cyclopropyl-substituted alkynes†

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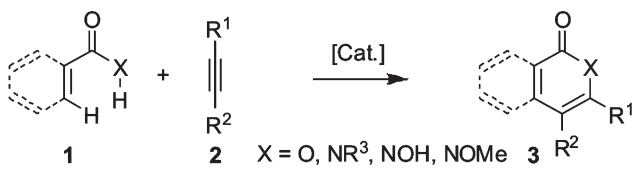
The chemical behavior of cyclopropyl-substituted alkynes has been probed using the reaction conditions of ruthenium-catalyzed oxidative C–H/O–H and C–H/N–H bond functionalizations. The oxidative annulations proceeded with complete conservation of all cyclopropane fragments and allowed for the one-step preparation of synthetically useful cyclopropyl-substituted isocoumarins and isoquinolones with high regioselectivities and chemical yields. The connectivities of the key heterocyclic products were unambiguously established by X-ray diffraction analysis.



## Introduction

Transition metal-catalyzed reactions have matured to being among the most powerful tools in organic chemistry.[1] Particularly, direct functionalizations[2] of aromatic C–H bonds have received considerable recent attention as ecologically and economically friendly synthetic methods, that avoid the use of prefunctionalized starting materials. Yet, an even more sustainable strategy is represented by the simultaneous transition metal-catalyzed C–H/O–H or C–H/N–H bond functionalizations utilizing arenes or alkenes **1** (Scheme 1).

This approach allowed for the one-pot preparation of synthetically useful heterocycles **3**, such as substituted isoquinolinones, isoquinolones, isocoumarins, α-pyrones and 2-pyridones, many of which possess valuable biological activities[3a–e] and represent key structural scaffolds of naturally occurring compounds.[3f–l] Consequently, a number of valuable protocols for intermolecular oxidative annulations with alkynes **2** have been developed,[4,5] with ruthenium-catalyzed[4] cyclizations being among the most promising.




**1** **2** **3**

**Scheme 1** Oxidative annulations by C–H/O–H or C–H/N–H bond functionalizations.

The attachment of a cyclopropyl fragment to heterocyclic molecules frequently modifies their pharmacological properties and significantly enhances their biological activities.[6] For instance, a number of well-known antibacterial agents, such as Ciprofloxacin, Sparfloxacin, Grepafloxacin and WIN-57294, contain a 1-cyclopropylquinolin-4(1*H*)-one moiety.[6e,f] However, the inherently high molecular strain in cyclopropanes (28.1 kcal mol$^{-1}$)[7] is reflected by some specificity to the chemistry of cyclopropane-containing molecules. As a consequence, metal-mediated or -catalyzed reactions with participation of (cyclopropylcarbinyl) metal intermediates proceeded almost exclusively *via* opening of at least one cyclopropane ring,[8] whereas formation of cyclopropane-containing compounds was observed as a side reaction only. Given the remarkable biological activity of cyclopropyl-decorated heterocycles along with the challenges associated with the use of cyclopropyl-substituted alkynes **2** in transition-metal catalysis, we, thus, became attracted to exploring their unprecedented oxidative annulations by metal-catalyzed C–H/Het–H bond functionalization with rather inexpensive ruthenium catalysts, on which we wish to report herein.

## Results and discussion

To elucidate the synthetic versatility of the transformation as well as the influence and reactivity of cyclopropyl substituents

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†Electronic supplementary information (ESI) available: Experimental details of syntheses and X-ray diffraction, $^{1}$H NMR spectra and $^{13}$C NMR spectra of new compounds. CCDC 901337 (**6aa**), 901338 (**6ae**), 901339 (**7aa**), 901340 (**8aa**) and 901341 (**8ah**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob26250a

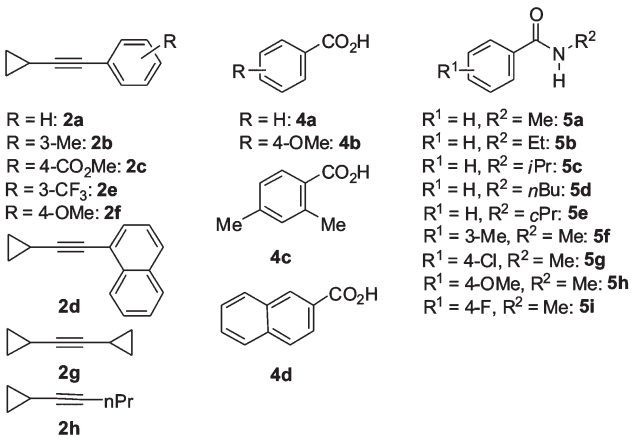
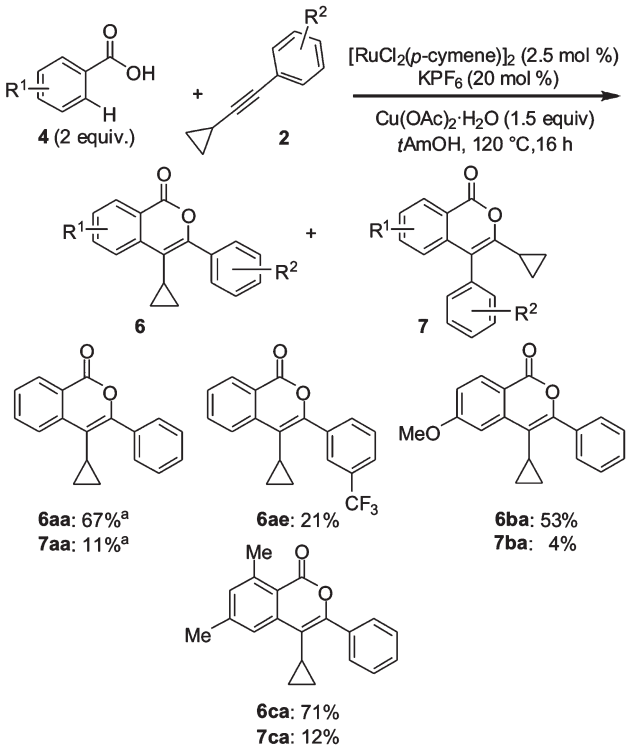



**Fig. 1** Substituted ethynylcyclopropanes **2**, benzoic acids **4** and benzamides **5** used in C–H/Het–H bond functionalizations.

in the alkynes **2**, we set out to perform detailed synthetic and structural studies on atom- and step-economical ruthenium-catalyzed C–H/O–H and C–H/N–H bond functionalizations of representative benzoic acids **4a–d** and benzamides **5a–i** with various cyclopropylacetylenes **2** (Fig. 1).

We initiated our studies by exploring the reactivity of substituted benzoic acids **4** and cyclopropylarylethynes **2** in ruthenium-catalyzed oxidative annulations[4f] (Scheme 2). Notably, arylalkynes displaying a cyclopropyl substituent yielded the desired product through the C–H/O–H bond functionalizations

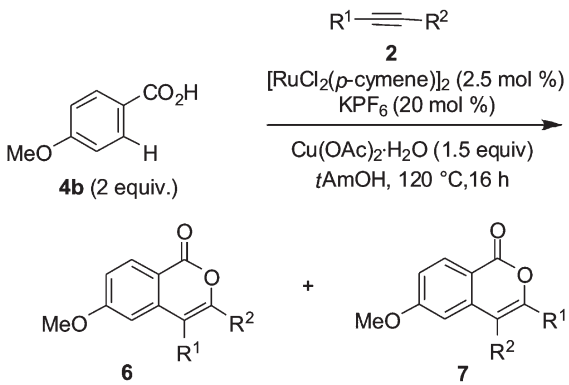



**Scheme 2** Ruthenium-catalyzed C–H/O–H bond functionalizations with benzoic acids **4** and (cyclopropylethynyl)benzenes **2**. [a][RuCl$_2$(*p*-cymene)]$_2$ (5 mol %).

reaction manifold. Thus, the highest yield was observed for the alkyne **2a** in the reaction with the acid **4c**, while the yield decreased with alkyne **2e** possessing an electron-withdrawing substituent. However, the influence of the substituents in benzoic acids **4** was found to be less pronounced.

No product formation was observed in the reactions of substrate **4a** with alkyne **2d** and when using starting materials **4d** and **2a**, while the corresponding isocoumarin **6dk** was formed in the reaction of **4d** with diethylethyne in 31% yield.†

The influence of the cyclopropyl moieties upon the course of chemical transformations by the stabilization of key reaction intermediates due to conjugation is well documented.[9] However, several representative experiments with *p*-anisic acid (**4b**) and selected alkynes **2** (Table 1) indicated the cyclopropyl substituents in the alkynes **2** to translate into a reduction of their reactivity (entry 1), but demonstrated no significant influence onto the regioselectivity of the annulation. Indeed, the reaction with (pent-1-ynyl)cyclopropane (**2h**) furnished a 1 : 1 mixture of the two regioisomeric isocoumarins **6bh** and **7bh** (entry 2), thereby indicating a negligible effect of steric interactions[10] in these annulations. Furthermore, the electronic effect of the cyclopropane appeared to be of less importance for the overall regioselectivity.




It is noteworthy that the rhodium-catalyzed annulation of unsymmetrically substituted arylalkyl alkynes Alk–C≡C–Ar delivered mixtures of 3- and 4-arylsubstituted regioisomeric products[11,12] in ratios of 6 : 1 to 8 : 1.[5i,j] In spite of the previously reported almost exclusive formation of 3-arylsubstituted products,[4e] the cyclization of alkyne **2i** afforded in our hands heterocycles **7bi** and **6bi** in a ratio of 9.4 : 1 (Table 1, entry 3).

In the ruthenium-catalyzed cyclizations of unsymmetrical cyclopropylacetylenes the ratios of regioisomeric products **6** and **7** varied from 1 : 1 to 13 : 1 (Scheme 2 and Table 1). To

**Table 1** Ruthenium-catalyzed C–H/O–H bond functionalizations with *p*-anisic acid (**4b**) and selected substituted alkynes **2**

| Entry | Alkyne | $R^1$ | $R^2$ | Product **6**/yield (%) | Product **7**/yield (%) |
|---|---|---|---|---|---|
| 1 | **2g** | *c*Pr | *c*Pr | **6bg** = **7bg** | **7bg**/27 |
| 2 | **2h** | *c*Pr | *n*Pr | **6bh**/**7bh** 1 : 1/53 | |
| 3 | **2i** | Et | Ph | **6bi**/47 | **7bi**/5 |

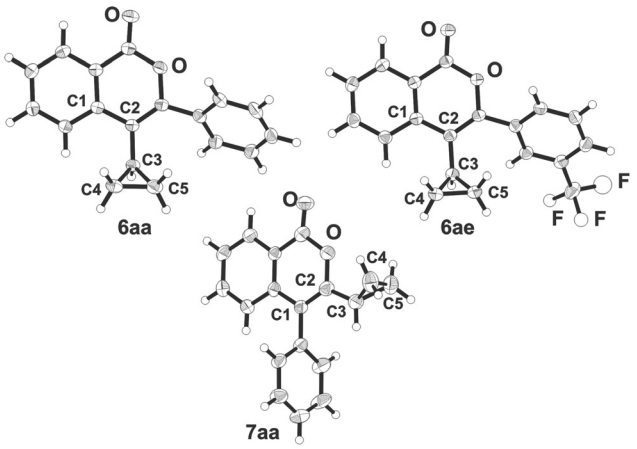


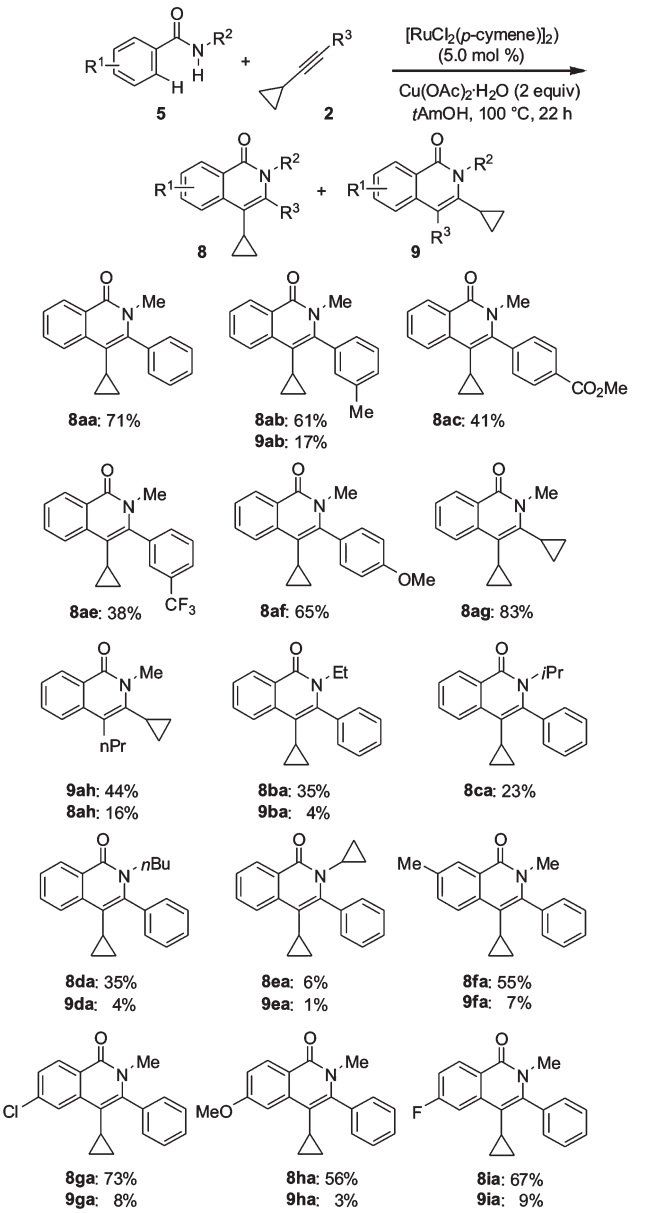

**Fig. 2** Molecular structures of isocoumarins **6aa**, **6ae** and **7aa** in the crystal[13] (numbering does not correspond to the IUPAC rules).

elaborate spectroscopic criteria† for this group of cyclopropyl-substituted heterocycles, the structures of cyclopropylisocoumarins **6aa**, **6ae** and **7aa** have been unambiguously established by X-ray diffraction analysis (Fig. 2). Notably, both 3-aryl-4-cyclopropyl-substituted heterocycles **6aa** and **6ae** adopted essentially the same conformations with the dihedral angles C1–C2–C3–center (C4–C5) being equal to −99.5° and −96.8°, respectively, while the dihedral angles between heterocyclic and carbocyclic aromatic moieties were found to be 47.3 and 37.6°, respectively. In contrast, in **7aa** the dihedral angle C1–C2–C3–centre (C4–C5) = 179.4° with the angle between aromatic planes of 66.5°, *i.e.* with almost ideal conditions for the conjugation of cyclopropyl and isocoumarin fragments.†

Somewhat similar tendencies were observed in ruthenium-catalyzed C–H/N–H bond functionalizations in benzamides **5** with (cyclopropylethynyl)benzenes **2**, the results of which are summarized in Scheme 3. Generally, the oxidative annulations occurred with high yields and synthetically useful regioselectivity. While the catalytic system displayed a high functional group tolerance, the attempted cyclization of amide **5a** with cyclopropylnaphthylalkyne **2d** gave less satisfactory results.† Furthermore, cyclopropylaryl alkynes **2c** and **2e** possessing electron-withdrawing substituents on the aromatic rings delivered the corresponding products **8ac** and **8ae**, respectively, in somewhat lower yield. However, a number of oxidative cyclizations, including the reaction of the parent compounds **2a** and **5a**, proceeded in a regiospecific manner affording only regioisomers **8** (**8aa**, **8ac**, **8ae**, **8af** and **8ca**), while in the other cases the ratio of heterocycles **8** and **9** varied from 9.8 (**8ia**) to 3.6 (**8ab**). Surprisingly, the best yield (83%) was obtained when utilizing dicyclopropylacetylene (**2g**), which was less reactive in the ruthenium-catalyzed isocoumarin synthesis (*vide supra*). Unfortunately, the attempted synthesis of *N*-cyclopropyl-3(4)-cyclopropylisoquinolones **8ea** and **9ea** occurred less efficiently. Moreover, the benzamide **5e** did not react with diphenylacetylene (tolane) under otherwise identical reaction conditions.

Remarkably, the nitrogen substituent had a considerable effect on the outcome of the annulation. Thus, *N*-Me- (**5a**), *N*-Et- (**5b**), *N*-*n*Bu- (**5d**) and *N*-iso-propylbenzamides (**5c**) furnished the corresponding isoquinolones **8** and **9** in the reactions with the alkyne **2a** in 71, 39, 39 and 23% yield, respectively. This is in line with the values of steric substituent constants of these alkyl groups, which are equal to 0, 0.86, 0.86 and 2.29, respectively.[10] Yet, in contrast to the synthesis of isocoumarins, the reaction of cyclopropyl-*n*-propyl alkyne (**2h**) with benzamide **5a** afforded a 2.75 : 1 mixture of 3-cyclopropyl (**9ah**) and 4-cyclopropylisoquinolones (**8ah**) (Scheme 3), in spite of the steric substituent constants being equal to 0.89 (*n*-propyl) and 1.33 (cyclopropyl).[10]

The exact connectivities of the parent isoquinolone **8aa** and of the fundamentally important compound **8ah** have been established by X-ray diffraction analysis (Fig. 3). As for the




**Scheme 3** Ruthenium-catalyzed C–H/N–H bond functionalizations in benzamides **5** with (cyclopropylethynyl)benzenes **2**.

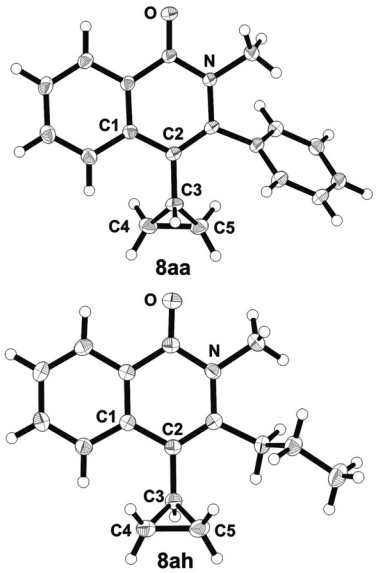
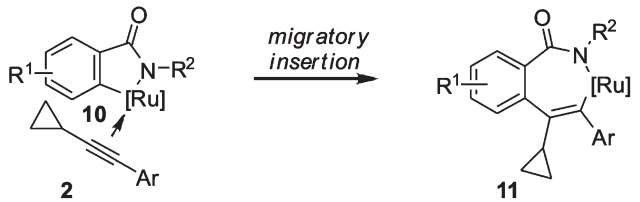



**Fig. 3** Molecular structures of isoquinolones **8aa** and **8ah** in the crystal[13] (numbering does not correspond to the IUPAC rules).




**Scheme 4** Regiochemistry-determining step of the ruthenium-catalyzed C–H/Het–H and C–H/N–H bond functionalizations.

analogous isocoumarins **6aa** and **6ae**, heterocycles **9aa** and **9ah** adopted essentially the same conformations with the dihedral angles C1–C2–C3–center (C4–C5) equal to 94.7° and 91.7°, respectively, *i.e.* without steric preconditions for conjugation, while the dihedral angle between heterocyclic and phenyl aromatic moieties in **8aa** was determined to be 63.2°.

It is particularly noteworthy that all the ruthenium-catalyzed oxidative C–H/Het–H bond functionalizations proceeded with complete conservation of all cyclopropane fragments.[8,14] As a consequence, cyclopropylethynes can be utilized in ruthenium-catalyzed C–H/Het–H bond functionalizations for the preparation of valuable cyclopropyl-substituted heterocycles. According to the mechanistic rationalizations generally accepted for ruthenium-catalyzed C–H/Het–H bond functionalization with alkynes,[4a,b,d–g] the regiochemistry-determining step of these oxidative reactions is constituted by the insertion of alkyne **2** into the ruthenium–carbon bond of key intermediate **10** to give the seven-membered ruthenacycle **11** (Scheme 4). Thus, the observed regioselectivities can for instance be rationalized by the enhanced thermodynamic stability of regioisomer **11**, in which the aryl substituent is in the neighboring position to the ruthenium.

## Conclusions

In summary, we have examined the behavior of cyclopropyl-substituted acetylenes in the ruthenium-catalyzed oxidative C–H/O–H and C–H/N–H bond functionalizations and have found these reactions to proceed with complete conservation of all cyclopropane fragments. Thereby, these cyclizations allowed the one-step preparation of synthetically useful cyclopropyl-substituted isocoumarins and isoquinolones in high yields and regioselectivities.[15]

## Experimental

### Syntheses: general methods

Catalytic reactions were carried out using pre-dried glassware. Triethylamine and *t*AmOH were distilled over $CaH_2$ and sodium, respectively. Anhydrous THF was obtained by distillation over sodium benzophenone ketyl. (Cyclopropylethynyl) benzene (**2a**), 1-(cyclopropylethynyl)-3-methylbenzene (**2b**), methyl 4-(cyclopropylethynyl)benzoate (**2c**), 1-(cyclopropylethynyl)naphthalene (**2d**), 1-(cyclopropylethynyl)-4-methoxylbenzene (**2f**), the previously unknown 1-(cyclopropylethynyl)-3-(trifluoromethyl)benzene (**2e**), (pent-1-ynyl)cyclopropane (**2h**), 1,2-dicyclopropylethyne (**2g**), *N*-cyclopropylbenzamide (**5e**), *N*,3-dimethylbenzamide (**5f**), 4-chloro-*N*-methylbenzamide (**5g**), 4-methoxy-*N*-methylbenzamide (**5h**), 4-fluoro-*N*-methylbenzamide (**5i**) and $[RuCl_2(p\text{-cymene})]_2$ were synthesized as indicated in the ESI.† Other chemicals were obtained from commercial sources and were used without further purification. Yields refer to isolated compounds, estimated to be >95% pure as determined by $^1$H-NMR and GC. TLC: Macherey-Nagel, TLC plates Alugram® Sil G/$UV_{254}$. Detection under UV light at 254 nm. Chromatography: Separations were carried out on Merck Silica 60 (0.040–0.063 mm, 70–230 mesh ASTM). All IR spectra were recorded on a BRUKER ALPHA-P spectrometer. MS: EI-MS: Finnigan MAT 95, 70 eV; ESI-MS: Finnigan LCQ. High resolution mass spectrometry (HRMS): APEX IV 7T FTICR, Bruker Daltonic. M.p.: Stuart® Melting Point Apparatus SMP3 melting point apparatus, values are uncorrected. $^1$H, $^{13}$C, $^{19}$F NMR-spectra were recorded at 300 ($^1$H), 75.5 {$^{13}$C, APT (Attached Proton Test)} and 283 MHz ($^{19}$F), respectively, on a Varian Unity-300 instrument.

### Synthesis of cyclopropyl-substituted isocoumarins 6 and 7

General procedure for ruthenium-catalyzed C–H/O–H bond functionalizations in benzoic acids 4 with ethynylbenzenes 2. A suspension of acid **4** (2.00 mmol), alkyne **2** (1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.5 mg, 2.5 mol%), $KPF_6$ (36.8 mg, 20 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (300 mg, 1.50 mmol) in *t*AmOH (3.0 mL) was stirred at 120 °C for 16 h. After cooling to ambient temperature, the reaction mixture was diluted with sat. aq. $NH_4Cl$–$NH_3$ solution (1 : 1, 50 mL) and extracted with EtOAc (4 × 25 mL). The combined organic layers were washed with $NH_4Cl$–$NH_3$ solution (1 : 1, 2 × 20 mL) and dried over $MgSO_4$. After filtration and concentration of the solution under reduced

pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane–EtOAc 25 : 1) to yield **6** and **7** as colorless solids.

4-Cyclopropyl-3-phenyl-1*H*-isochromen-1-one (6aa) and 3-cyclopropyl-4-phenyl-1*H*-isochromen-1-one (7aa). According to the general procedure, benzoic acid (**4a**) (490 mg, 4.0 mmol), alkyne (**2a**) (284 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (62.0 mg, 100 μmol), $KPF_6$ (73 mg, 0.4 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (599 mg, 3.0 mmol) yielded compounds **6aa** (353 mg, 67%) and **7aa** (64 mg, 11%) as colorless solids. **6aa**: m.p. = 115–117 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 8.33 (dd, $J$ = 8.0, 1.4 Hz, 1H), 8.12 (d, $J$ = 8.2, 1H), 7.78 (td, $J$ = 7.7, 1.41 Hz, 1H), 7.76–7.72 (m, 2H), 7.50 (td, $J$ = 7.7, 1.1 Hz, 1H), 7.46–7.37 (m, 3H), 1.91 (tt, $J$ = 8.1, 5.5 Hz, 1H), 1.00–0.87 (m, 2H), 0.26–0.06 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 162.4 (C), 153.4 (C), 139.7 (C), 134.4 (CH), 133.2 (C), 129.5 (CH), 129.4 (CH), 129.3 (CH), 127.8 (CH), 127.7 (CH), 124.5 (CH), 120.6 (C), 114.5 (C), 9.9 ($CH_2$), 9.0 (CH); IR (ATR): 3011, 2961, 2922, 2855, 1718, 1629, 1078, 700 cm$^{-1}$; MS (EI) $m/z$ (%): 262 ($M^+$, 100), 247 (50), 234 (35), 165 (65), 69 (25); HRMS (EI) $m/z$ calcd for $C_{18}H_{14}O_2$ ($M^+$) 262.0994, found 262.0988.

**7aa**: m.p. = 100–102 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 8.20 (dd, $J$ = 7.9, 1.6 Hz, 1H), 7.57–7.33 (m, 7H), 6.95 (ddd, $J$ = 8.1, 1.1, 0.5 Hz, 1H), 1.70–1.56 (m, 1H), 1.21–1.12 (m, 2H), 0.81–0.70 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 162.0 (C), 154.2 (C), 138.8 (C), 134.4 (CH), 134.2 (C), 131.0 (2CH), 129.3 (CH), 128.8 (CH), 127.9 (CH), 126.7 (CH), 123.9 (CH), 119.5 (C), 115.0 (C), 12.0 (CH), 7.6 ($CH_2$); IR (ATR): 3084, 3049, 3008, 2984, 1727, 1604, 1075, 672 cm$^{-1}$; MS (EI) $m/z$ (relative intensity): 262 ($M^+$, 50), 217 (45), 185 (40), 105 (55), 77 (100); HRMS (EI) calcd for $C_{18}H_{14}O_2$ ($M^+$) 262.0994, found 262.0996.

The connectivities of compounds **6aa** and **7aa** were established by X-ray crystal structure analysis.[13]

4-Cyclopropyl-6-methoxy-3-phenyl-1*H*-isochromen-1-one (6ba) and 3-cyclopropyl-6-methoxy-4-phenyl-1*H*-isochromen-1-one (7ba). According to the general procedure, *p*-anisic acid (**4b**) (152 mg, 4.0 mmol), alkyne **2a** (284 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 μmol), $KPF_6$ (73 mg, 0.4 mmol) and $Cu(OAc)_2{\cdot}H_2O$ (599 mg, 3.0 mmol) yielded **6ba** (308 mg, 53%) and **7ba** (23 mg, 4%) after column chromatography as colorless solids. **6ba**: m.p. = 144–146 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 8.27 (d, $J$ = 8.8 Hz, 1H), 7.75–7.71 (m, 1H), 7.50 (d, $J$ = 2.5 Hz, 1H), 7.46–7.40 (m, 2H), 7.06 (dd, $J$ = 8.8, 2.5 Hz, 1H), 3.97 (s, 2H), 1.88 (tt, $J$ = 8.1, 5.5 Hz, 1H), 0.98–0.88 (m, 1H), 0.23–0.15 (m, 1H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 164.6 (C), 162.3 (C), 154.2 (C), 142.2 (C), 133.4 (C), 131.9 (CH), 129.6 (CH), 129.6 (CH), 129.5 (CH), 127.9 (CH), 115.5 (CH), 114.4 (C), 113.9 (C), 107.7 (CH), 55.7 ($CH_3$), 10.0 ($CH_2$), 9.2 (CH); IR (ATR): 3005, 2956, 2856, 1711, 1600, 1444, 1226, 831 cm$^{-1}$; MS (EI) $m/z$ (%): 292 ($M^+$, 95), 217 (36), 215 (77), 105 (90), 77 (100); HRMS (EI) calcd for $C_{19}H_{16}O_3$ ($M^+$) 292.1099; found 292.1099.

**7ba**: m.p. = 126–128 °C; $^1$H NMR (300 MHz, $CDCL_3$) $\delta$ = 8.22 (d, $J$ = 8.8 Hz, 1H), 7.54–7.34 (m, 5H), 6.94 (dd, $J$ = 8.8, 2.5 Hz, 1H), 6.35 (d, $J$ = 2.5 Hz, 1H), 3.72 (s, 3H), 1.67–1.55 (m, 1H), 1.23–1.13 (m, 2H), 0.85–0.74 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 164.6 (C), 161.9 (C), 155.0 (C), 141.4 (C), 134.5 (C), 131.9 (CH), 131.1 (CH), 129.0 (CH), 128.0 (C), 115.1 (C), 114.6 (CH), 113 0 (C), 107.1 (CH), 55.6 ($CH_3$), 12.2 (CH), 7.8 ($CH_2$); IR (ATR): 3009, 2925, 1713, 1600, 1231, 1044, 849, 723 cm$^{-1}$; MS (EI) $m/z$ (%): 292 ($M^+$, 100), 277 (32), 264 (55), 195 (35), 152 (50); HRMS (EI) calcd for $C_{19}H_{16}O_3$ ($M^+$) 292.1099, found 292.1105.

## Synthesis of cyclopropyl-substituted isoquinolones 8 and 9

General procedure for ruthenium-catalyzed C–H/N–H bonds functionalizations in benzamides 5 with (cyclopropylethynyl)benzenes 2. A mixture of benzamide **5** (0.50 mmol), acetylene **2** (1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 25 μmol, 5.0 mol%) and $Cu(OAc)_2{\cdot}H_2O$ (200 mg, 1.00 mmol) in *t*AmOH (2.0 mL) was stirred at 100 °C under a nitrogen atmosphere for 22 h. After cooling the mixture to ambient temperature, the reaction mixture was diluted with aq. $NH_3$ solution (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 $Mg_2SO_4$. After filtration and concentration of the solution under reduced pressure, the crude product was purified by column chromatography on silica gel (*n*-hexane–EtOAc 4 : 1) to yield **8** and **9** as colorless solids.

4-Cyclopropyl-2-methyl-3-phenylisoquinolin-1(2*H*)-one (8aa). According to the general procedure, *N*-methylbenzamide (**5a**) (135 mg, 1.0 mmol), alkyne **2a** (284 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 μmol), and $Cu(OAc)_2{\cdot}H_2O$ (399 mg, 2.0 mmol) yielded **8aa** (185 mg, 71%) after column chromatography as a colorless solid, m.p. = 139–141 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 8.49 (ddd, $J$ = 8.0, 1.5, 0.6 Hz, 1H), 8.19 (ddd, $J$ = 8.3, 1.2, 0.6 Hz, 1H), 7.68 (ddd, $J$ = 8.4, 7.1, 1.5 Hz, 1H), 7.51–7.39 (m, 4H), 7.31–7.27 (m, 2H), 3.28 (s, 3H), 1.62 (tt, $J$ = 8.3, 5.6 Hz, 1H), 0.69–0.55 (m, 2H), 0.17–0.05 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 162.8 (C), 142.9 (C), 138.0 (C), 135.7 (C), 133.7 (CH), 129.9 (CH), 128.4 (CH), 128.4 (CH), 127.9 (CH), 126.2 (CH), 125.1 (C), 124.4 (CH), 115.0 (C), 34.2 ($CH_3$), 10.5 (CH), 8.7 ($CH_2$); IR (ATR): 3081, 2994, 2957, 2924, 1643, 1587, 1025, 759 cm$^{-1}$. MS (EI) $m/z$ (%): 275 ($M^+$, 32), 274 (100), 246 (15), 198 (27), 77 (30); HRMS (EI) calcd for $C_{19}H_{17}NO$ ($M^+$) 275.1310, found 275.1298. The structure of compound **8aa** was established by X-ray crystal structure analysis.[13]

4-Cyclopropyl-6-methoxy-2-methyl-3-phenylisoquinolin-1(2*H*)-one (8ha) and 3-cyclopropyl-6-methoxy-2-methyl-4-phenylisoquinolin-1-(2*H*)-one (9ha). According to the general procedure, 4-methoxy-*N*-methylbenzamide (**5h**) (165 mg, 1.0 mmol), alkyne **2a** (284 mg, 2.0 mmol), $[RuCl_2(p\text{-cymene})]_2$ (31 mg, 50 μmol), and $Cu(OAc)_2{\cdot}H_2O$ (399 mg, 2.0 mmol) yielded **8ha** (173 mg, 56%) and **9ha** (9 mg, 3%) after column chromatography as colorless solids. **8ha**: m.p. = 135–137 °C; $^1$H NMR (300 MHz, $CDCl_3$) $\delta$ = 8.39 (d, $J$ = 8.9 Hz, 1H), 7.53 (d, $J$ = 2.5 Hz, 1H), 7.48–7.37 (m, 3H), 7.29–7.23 (m, 2H), 7.04 (dd, $J$ = 8.9, 2.5 Hz, 1H), 3.91 (d, $J$ = 1.5 Hz, 3H), 3.24 (d, $J$ = 1.4 Hz, 3H), 1.57 (tt, $J$ = 8.2, 5.6 Hz, 1H), 0.63–0.54 (m, 2H), 0.13–0.05 (m, 2H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 162.3 (C), 162.2 (C), 143.5 (C), 140.0 (C), 135.6 (C), 129.9 (CH), 129.8 (CH), 128.3 (CH), 119.0 (C), 115.1 (C), 114.4 (C), 109.1 (C), 106.9 (CH), 55.2 ($CH_3$), 33.9 ($CH_3$), 10.4 (CH), 8.6 ($CH_2$); IR (ATR): 2991, 2939, 2914, 1639, 1604, 1275, 1027, 779,

725, 687 $cm^{-1}$; MS (EI) *m*/*z* (%): 305 ($M^+$, 52), 304 (84), 274 (100), 228 (68), 185 (20), 118 (30), 84 (40), 77 (46); HRMS (EI) calcd for $C_{20}H_{19}NO_2$ ($M^+$) 305.1416; found: 305.1416.

**9ha**: m.p. = 145–147 °C; $^1H$ NMR (300 MHz, $CDCl_3$) $\delta$ = 8.39 (d, *J* = 8.9 Hz, 1H), 7.47–7.33 (m, 3H), 7.28 (d, *J* = 1.7 Hz, 1H), 7.25 (t, *J* = 1.5 Hz, 1H), 6.99 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.59 (d, *J* = 2.5 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 3H), 1.72 (tt, *J* = 8.3, 5.7 Hz, 1H), 0.75–0.66 (m, 2H), 0.34–0.25 (m, 2H); $^{13}C$ NMR (75 MHz, $CDCl_3$) $\delta$ = 162.6 (C), 162.3 (C), 140.8 (C), 138.9 (C), 137.3(C), 131.4 ($CH_2$), 129.9 (CH), 128.3 (CH), 127.1 (CH), 119.4 (C), 118.7 (C), 115.0 (CH), 106.5 (CH), 55.2 ($CH_3$), 32.1 ($CH_3$), 14.0 (CH), 10.2 ($CH_2$); IR (ATR): 3057, 2974, 2939, 2914, 1643, 1586, 1225, 1025, 781, 705 $cm^{-1}$; MS (EI) *m*/*z* (%): 305 ($M^+$, 94), 290 (100), 277 (33), 152 (21), 82 (13), 41 (10); HRMS (EI) calcd for $C_{20}H_{19}NO_2$ ($M^+$) 305.1416; found: 305.1417.

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