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Metal-free Catalyzed Cyclization of *N*-methoxybenzamides to Construct Quaternary Carbon-Containing Isoindolinones

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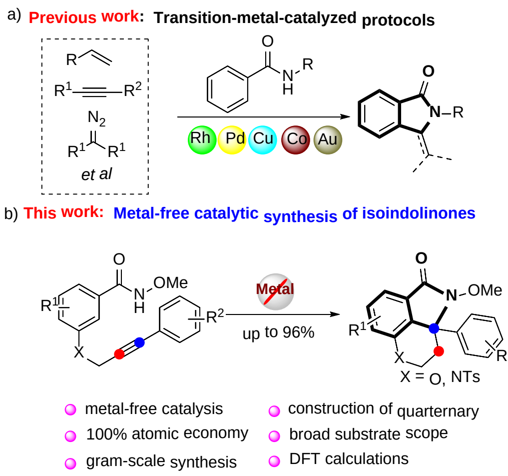
Summary of main observation and conclusion Through the intramolecular cyclization of *N*-methoxybenzamides, a simple and efficient method for constructing valuable isoindolinones under metal-free conditions was developed. The reaction was featured by employing low-cost catalyst, simple operation, 100% atomic economy and excellent regioselectivity. Moreover, a detailed computational study on the reaction system has been performed to clarify the mechanism. This protocol tolerated a variety of functional groups and provided a metal-free protocol for the synthesis of chromane- or tetrahydroquinoline-fused isoindolinones in good yields.

Background and Originality Content

Among the large family of indoles, isoindolinone derivatives are remarkable owing to their prevalence in natural products, drugs and functional materials. For example, indoprofen is used in anti-inflammatory drugs, falipamil demonstrates anti-ischemic properties, chlortalidone has a diuretic effect and pestalachloride A is identified as an antifungal drug.[1] Therefore, the synthesis of this class of compounds caused a great interest of chemists, and various synthetic methods have been developed.[2]

Scheme 1 The synthetic methods for isoindolinones.

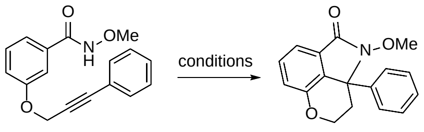


Remarkable progress has been made in the Rh(III)-, Pd(II)-, Cu(II)-, Co(II)- and Au(I)-catalyzed C–H bond functionalizations, which provides a step- and atom-economical route to isoindolinones from less functionalized substrates (Scheme 1a).[3] For instance, the group of Ma reported the Rh(III)-catalyzed synthetic route of isoindolinones via a sequential C–H activation/allene formation/cyclization pathway.[4] We disclosed a Co/Ag-catalyzed C-H alkynylation/annulation with alkynes for the construction of 3-methyleneisoindolinones.[5] Despite the fact that significant development has been achieved on transition metals promoting research of the cyclization of alkynes based on C-H functionalizations or cascade reactions, an alternative route relying on metal-free strategy to construct target products is still appealing due to green and economy features.[6]

Triflimide ($HNTf_2$) as a special catalyst has been achieved uniquely outstanding performance in a range of organic transformations, including C–C and C-heteroatom formation processes because of its strong acidity and good compatibility with organic solvents.[7] In these cases, it has been extensively used as a super Brønsted acid to catalyze Friedel–Crafts reactions,[8] aldol reactions,[9] and cycloaddition reactions.[10] Especially, Ye and co-workers have developed a variety of $HNTf_2$-initiated cascade cyclizations of ynamides for the synthesis of functionalize heterocycle compounds based on keteniminium ions.[11] Inspired by these successful results and as part of our interest in green chemistry,[12] we envisioned that $HNTf_2$ might also active the simple alkynes, thus allowing the facile and practical access to a variety of highly functionalized isoindolinones. Herein, we describe the realization of intramolecular $HNTf_2$-initiated cascade cyclization of alkynes, leading to chromane-fused isoindolinones in good yields, providing a green and economical alternative among the previously applicable metal-catalyzed protocols (Scheme 1b).

Results and Discussion

Table 1 Optimization of reaction conditions for **3a**.[a]



1a **3a**

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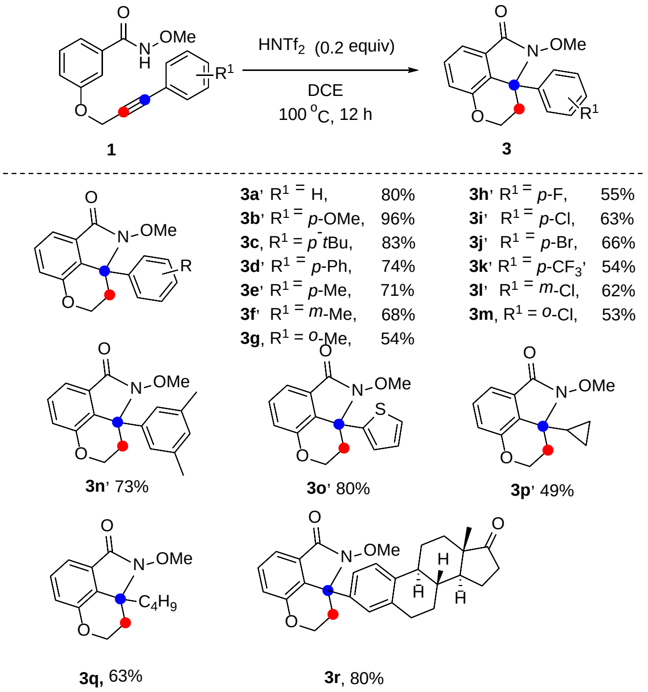
Entry	Catalyst **2**	Solvent	Temp (℃)	Yield (%)^b
1	AgOTf	DCE	100	29
2	$Cu(OTf)_2$	DCE	100	33
3	$Zn(OTf)_2$	DCE	100	36
4	$Sc(OTf)_3$	DCE	100	40
5	$In(OTf)_3$	DCE	100	51
6	$Yb(OTf)_3$	DCE	100	39
7	CF_3COOH	DCE	100	49
8	HOTf	DCE	100	63
9	$HNTf_2$	DCE	100	73
10	$HNTf_2$	DCM	100	64
11	$HNTf_2$	toluene	100	43
12	$HNTf_2$	MeOH	100	trace
13	$HNTf_2$	EtOH	100	trace
14	$HNTf_2$	HFIP	100	46
15	$HNTf_2$	DCE	80	60
16	$HNTf_2$	DCE	120	71
17^c	**$HNTf_2$**	**DCE**	**100**	**80**
18^d	$HNTf_2$	DCE	100	81
19^e	$HNTf_2$	DCE	100	82
20	-	DCE	100	n.r.^{f}

^{a}Reaction conditions: **1a** (0.1 mmol), catalyst **2** (0.01 mmol), solvent (2 mL), in air, 12 h. ^{b} Isolated yields. ^{c} 20 mol% of catalyst **2** was used. ^{d}25% mol of catalyst **2** was used. ^{e}100% mol of catalyst **2** was used. ^{f}n.r. = no reaction, DCE = 1,2-dichloroethane, HFIP = hexafluoroisopropanol.

At the outset, *N*-methoxy-3-((3-phenylprop-2-yn-1-yl)oxy)benzamide **1a** was employed as the model substrate to optimize the reaction conditions, and the results were summarized in Table 1. To our delight, the desired product **3a** was furnished in 29% yield when AgOTf was used as the catalyst in DCE under an air atmosphere at 100 °C (Table 1, entry 1). We then screened other cheap metal catalysts including copper-, zinc-, scandium-, indium- and ytterbium-salts (Table 1, entries 2–6) and found that $In(OTf)_3$ could efficiently catalyze the cascade cyclization, delivering the desired product **3a** in 51% yield (Table 1, entry 5). Further investigation of Brønsted acids revealed that $HNTf_2$ could effectively promote the reaction with a yield of 73% (Table 1, entries 7-9). The solvents have a significant influence on the transformation (Table 1, entries 10-14) and the protic solvents such as MeOH, EtOH and HFIP gave inferior yields. The reaction temperature was studied and the results showed that increasing or decreasing the temperature was not conducive to the reaction (Table 1, entries 15 and 16). Gratifyingly, by simple applying 20 mol% of $HNTf_2$ as a catalyst, the yields of **3a** could be further increased to 80%. The further increasement of the catalyst did not significantly promote the transformation with a better yield (Table 1, entries 18-19). A control experiment showed that $HNTf_2$ was essential to the transformation, and the reaction did not take place without it (Table 1, entry 20).

Under the existing conditions (Table 1, entry 17), the cyclization reaction of various alkyne-tethered *N*-methoxybenzamides **1** were explored. As shown in Scheme 2, the transformations proceeded smoothly and gave the corresponding products isoindolinones **3a**-**3r** with good to excellent yields. *N*-methoxybenzamides **1** with electron-donating substituents achieved excellent yields of 71–96% (**3b**-**3e**). However, *N*-methoxybenzamides **1** with electron-withdrawing groups such as F, Cl, Br and CF_3 showed slightly less reactive to provide 54–66% yields (**3h**-**3k**). For *meta*-substituted and *ortho*-substituted benzamides, the reaction is affected by the steric hindrance of the aromatic ring, both the electron-donating groups and the electron-withdrawing groups have inferior results with moderate yields (**3f**, **3g**, **3l** and **3m**). The reaction of the disubstituted benzamide **1n** proceeded smoothly, and the corresponding product **3n** was obtained in 73% yield. To our delight, heterocyclic substrate **1o** underwent smoothly to produce product **3o** in 80% yield. Additionally, the reaction with the alkyl-substituted substrates gave the products (**3p** and **3q**) in 49% and 63% yields, respectively. It is worth noting that natural product derivative **1r** could also be employed to provide corresponding product **3r** in a yield of 80%.

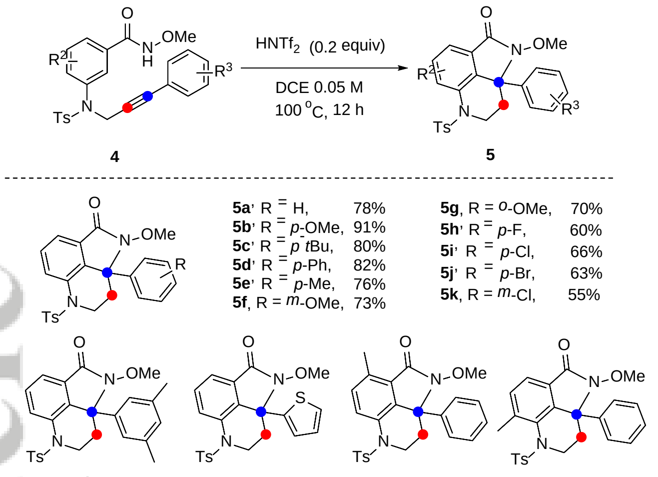
Scheme 2 Synthesis of isoindolinones **3**.^{a,b}



^{a}Reaction conditions: **1** (0.20 mmol), $HNTf_2$ (0.04 mmol), DCE (4 mL), 100 °C, 12 h. ^{b}Isolated yields.

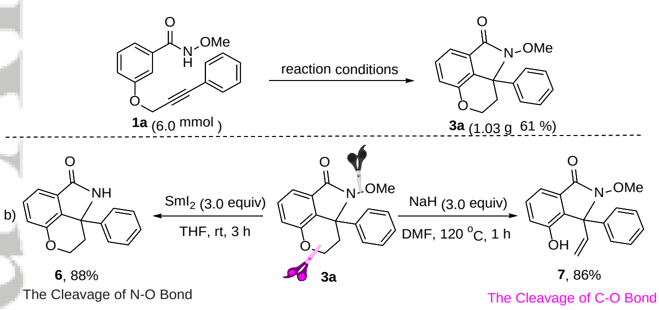
Next, the synthesis of tetrahydroquinoline-fused isoindolinones was also explored under the optimized reaction conditions by employing the aniline-typed *N*-methoxybenzamides **4** (Scheme 3). For R^3 groups, *N*-methoxybenzamides **4** with electron-donating substituents achieved good yields of 76–91% (**5b**-**5e**). Although the electronic effect on the aryl rings reduced the yields to some extent, the desired products **5h**–**5j** were still generated with yields ranging from 60% to 66%. Compared to *para*-substituted benzamides, the yields of *ortho*- and *meta*-substituents were slightly reduced (**5f**, **5g** and **5k**). The cyclization strategy was also compatible with disubstituted benzamide **4l**, and the product **5l** was got in 69% yield. Thiophene-substituted benzamide was also successfully converted to the corresponding heterocyclic product **5m** in 82% yield. For R^2 groups, when the methyl substituent was installed at *ortho* or *para* position of benzene ring, the desired isoindolinones were obtained in good yields (**5n** and **5o**)

Scheme 3 Synthesis of isoindolinones **5**.^{a,b}



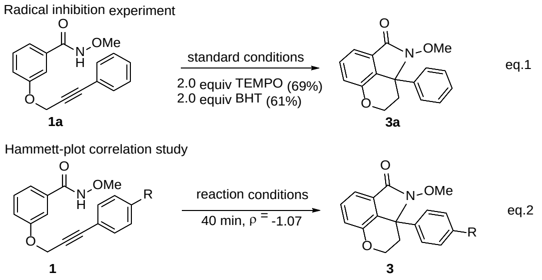
[a] Reaction conditions: **4** (0.20 mmol), HNTf₂ (0.04 mmol), DCE (4 mL), 100 °C, 12 h. [b] Isolated yields.

Scheme 4 Gram-scale experiment and synthetic application of **3a**.



To demonstrate the practical application of the present protocol, a gram-scale experiment was carried out for the reaction of **1a** (6 mmol) under the optimized reaction conditions, and **3a** was obtained in 61% yield (Scheme 4a). The product **3a** could be efficiently deprotected by treating with SmI$_2$ in THF, providing **6** in 88% yield, while the cleavage of C-O bond of **3a** by treatment with NaH in DMF produced the 4-hydroxyisoindolin-1-one **7** in 86% yield, which might have anti-HIV[13] and anti-inflammatory activities (Scheme 4b).[14]

Scheme 5 Control experiments.



The control experiments were performed to gain some understanding of the mechanism (Scheme 5). The addition of radical inhibitor into the reaction system provided **3a** smoothly, indicating that the radical pathway may not be involved in the process (Scheme 5, eq.1). Moreover, the reaction of different *para*-substituted *N*-methoxybenzamides **1** was studied (Scheme 5, eq.2). In the Hammett curve, lg(k_X/k_H) is linear with σ, and the negative value of ρ (-1.07) indicates that the reaction is facilitated by electron-donating groups (see Supporting information for details).[15]

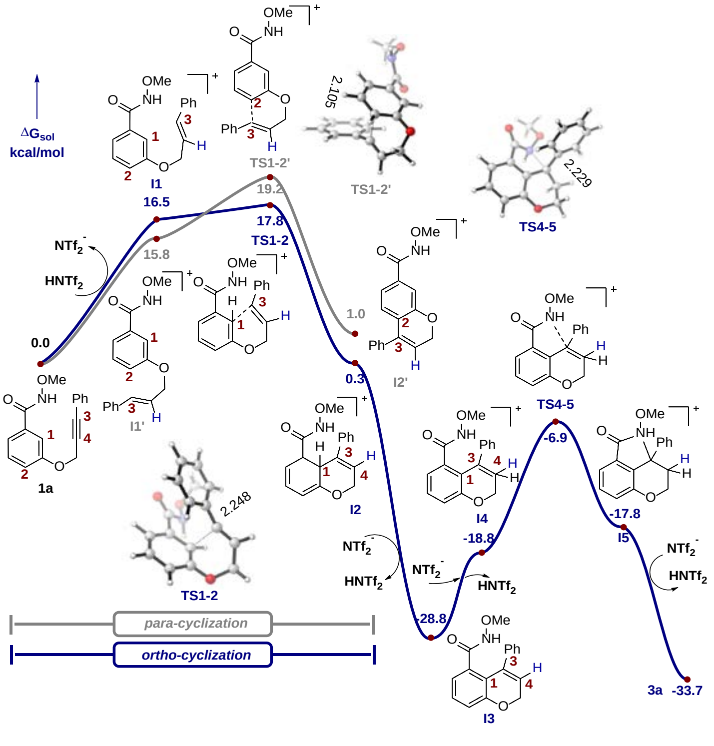


Figure 1 Calculated Gibbs free energy profiles for the possible reaction mechanism in kcal mol^{-1}

Moreover, density functional theory (DFT) calculations were performed to clarify the regioselectivity of the reaction (Figure 1; for the details see the Supporting Information). The initiation of the reaction involves the protonation of the alkynyl of **1a** to form a cationic intermediate **I1**, where the electrophilic *ortho*-cyclization process between the carbon cation C3 and C1 takes place via transition state **TS1-2** to afford **I2**.[16] The barrier needed for this step is 17.8 kcal mol^{-1}, which is affordable under the current experimental conditions. The electrophilic *para*-cyclization transition state **TS1-2'** was also located and the barrier is 1.4 kcal mol^{-1} higher than **TS1-2**, which agrees well with experimental results. The origin of the regioselectivity could be explained by the NBO charges in Figure 1. The NBO charges suggest that the electrostatic interaction between C1 and C3 in **TS1-2** is stronger than that between C2 and C3 in **TS1-2'**. This means that the C3 carbon would prefer to attack the C1 atom rather than C2 atom of the phenyl ring, generating the corresponding *ortho*-cyclization intermediate **I2**. From **I2**, the proton transfer from C1 to C4 (stepwise deprotonation and protonation via **I3,** moreover, a trace amount of **I3** was detected through HRMS) takes place with the help of NTf$_2^-$/HNTf$_2$ species, leading the reaction to intermediate **I4**, where the last ring closing process via C-N bond formation occurs. This is the rate-determining step with a reaction barrier of 21.9 kcal mol^{-1}. The desired product **3a** will be generated by the last deprotonation process. The whole reaction is exothermic about 33.7 kcal mol^{-1} with a rate-determining barrier of 21.9 kcal mol^{-1}, agreeing well with the experimental observations.

Conclusions

In conclusion, we have developed an efficient metal-free intramolecular cyclization of *N*-methoxybenzamides, enabling facile access to chromane- or tetrahydroquinoline-fused isoindolinones in good yields from easily available starting materials. This reaction was characterized by employing cheap catalyst, simple operation, broad substrate scope, 100% atomic economy and excellent regioselectivity. The gram-scale experiment rendered this method highly practical in organic synthesis. Moreover, a detailed computational study on the reaction system have been performed to clarify the mechanism. Further synthetic applications are currently undergoing in our laboratory.

Experimental

General experimental procedure for products 3a-3r and 5a-5o (using 3a as an example): To a stirred solution of *N*-methoxy-3-((3-phenylprop-2-yn-1-yl)oxy)benzamide **1a** (56.2 mg, 0.2 mmol) in DCE (4 mL) was added HNTf$_2$ (11.2 mg, 0.04 mmol) at room temperature in a sealing tube (10 mL). Next, the reaction mixture was sealed and heated at 100 °C for 12 h. Then, the solvent was evaporated in vacuum and purified by silica gel column chromatography to afford pure desired product **3a** (45 mg, 80%) as a yellow solid.

Supporting Information

The supporting information for this article is available on the WWW under https://doi.org/10.1002/cjoc.2018xxxxx.

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References

[1] (a) Ravikumar, K. Non-steroidal Anti-Inflammatory Drugs. III. Structure of Indoprofen: 2-[4-(1-oxo-2-isoindolinyl) phenyl] Propionic Acid. *Sect. C: Cryst. Struct. Commun.* **1994**, *50*, 589-592; (b). Reiffen, M.; Eberlein, W.; Muller, P.; Psiorz, M.; Noll, K.; Heider, J.; Lillie, C.; Kobinger, W.; Luger, P. Specific Bradycardic Agents. 1. Chemistry, Pharmacology, and Structure-Activity Relationships of Substituted Benzazepinones, a new Class of Compounds Exerting Antiischemic Properties. *J. Med. Chem.* **1990**, *33*, 1496-1504; (c) Volpe, R.; Mautner, L. S. Chlorthalidone, a new Oral Diuretic: Preliminary Report. *Appl. Ther.* **1961**, *3*, 521-528; (d) Li, E.-W.; Jiang, L.-H.; Guo, L.; Zhang, H.; Che, Y.-S. Pestalachlorides A–C, Antifungal Metabolites from the Plant Endophytic Fungus Pestalotiopsis Adusta. *Bioorg. Med. Chem.* **2008**, *16*, 7894-7899.

[2] (a) Glavac, D.; Zheng, C.; Dokli, I.; You, S.-Li.; Gredicak, M. Chiral Brønsted Acid Catalyzed Enantioselective aza-Friedel–Crafts Reaction of Cyclic α-Diaryl *N*-Acyl Imines with Indoles. *J. Org. Chem.* **2017**, *82*, 8752−8760; (b) Ray, S. K.; Sadhu, M. M.; Biswas, R. G.; Unhale, R. A.; Singh, V. K. A General Catalytic Route to Enantioenriched Isoindolinones and Phthalides: Application in the Synthesis of (S)-PD 172938. *Org. Lett*. **2019**, *21*, 417−422.

[3] (a) Wang, F.; Song, G.-Y.; Li, X.-W. Rh(III)-Catalyzed Tandem Oxidative Olefination−Michael Reactions between Aryl Carboxamides and Alkenes. *Org. Lett*. **2010**, *12*, 5430–5433; (b) Hyster, T. K.; Ruhl, K. E.; Rovis, T. A Coupling of Benzamides and Donor/Acceptor Diazo Compounds To Form γ-Lactams via Rh(III)-Catalyzed C–H Activation. *J. Am. Chem. Soc.* **2013**, *135*, 5364–5367; (c) Ye, B.-H.; Cramer, N. Asymmetric Synthesis of Isoindolones by Chiral Cyclopentadienyl-Rhodium(III)-Catalyzed C-H Functionalizations. *Angew. Chem. Int. Ed.* **2014**, *53*, 7896–7899; (d) Dong, J.-X.; Wang, F.; You, J.-S. Copper-Mediated Tandem Oxidative C(sp^2)–H/C(sp)–H Alkynylation and Annulation of Arenes with Terminal Alkynes. *Org. Lett.* **2014**, *16*, 2884–2887; (e) Zhang, Y.; Wang, D.-H.; Cui, S.-L. Facile Synthesis of Isoindolinones via Rh(III)-Catalyzed One-Pot Reaction of Benzamides, Ketones, and Hydrazines. *Org. Lett.* **2015**, *17*, 2494–2497; f) Lu, Y.; Wang, H.-W.; Spangler, J. E.; Chen, K.; Cui, P.-P.; Zhao, Y.; Sun, W.-Y.; Yu, J.-Q. Rh(III)-Catalyzed C–H Olefination of *N*-pentafluoroaryl Benzamides using Air as the sole Oxidant. *Chem. Sci.* **2015**, *6*, 1923–1927; (g) Zhou, Z.; Liu, G.-X.; Lu, X.-Y. Regiocontrolled Coupling of Aromatic and Vinylic Amides with α-Allenols To Form γ-Lactams via Rhodium(III)-Catalyzed C–H Activation. *Org. Lett*. **2016**, *18*, 5668−5671; (h) Wu, X.-W.; Wang, B.; Zhou, Y.; Liu, H. Propargyl Alcohols as One-Carbon Synthons: Redox-Neutral Rhodium(III)-Catalyzed C–H Bond Activation for the Synthesis of Isoindolinones Bearing a Quaternary Carbon. *Org. Lett.* **2017**, *19*, 1294−1297; (i) Ji, W.-W.; Lin, E.; Li Q.-J.; Wang, H.-G. Heteroannulation Enabled by a Bimetallic Rh(III)/Ag(I) Relay Catalysis: Application in the Total Synthesis of Aristolactam BII. *Chem. Commun.* **2017**, *53*, 5665−5668; (j) Cheng, X.-F.; Wang, T.; Li, Y.; Wu, Y.; Sheng, J.; Wang, R.; Li, C.; Bian, K.-J.; Wang, X.-S. Palladium(II)-Catalyzed C(sp^2)–H Carbonylation of Sterically Hindered Amines with Carbon Monoxide. *Org. Lett*. **2018**, *20*, 6530−6533; (k) Fu, L.-Y.; Ying, J.; Qi, X.-X.; Peng, J.-B.; Wu, X.-F. Palladium-Catalyzed Carbonylative Synthesis of Isoindolinones from Benzylamines with TFBen as the CO Source. *J. Org. Chem*. **2019**, *84*, 1421−1429; (l) Lukasevics, L.; Cizikovs, A.; Grigorjeva, L. Synthesis of 3-Hydroxymethyl Isoindolinones via Cobalt-Catalyzed C(sp^2)–H Carbonylation of Phenylglycinol Derivatives. *Org. Lett*. **2020**, *22*, 2720–2723; (m) Tian, C.; Dhawa, U.; Scheremetjew, A.; Ackermann, L. Cupraelectro-Catalyzed Alkyne Annulation: Evidence for Distinct C–H Alkynylation and Decarboxylative C–H/C–C Manifolds. *ACS Catal*. **2019**, *9*, 7690−7696; (n) Ding, D.; Mou, T.; Feng, M.; Jiang, X.-F. Utility of Ligand Effect in Homogenous Gold Catalysis: Enabling Regiodivergent π-Bond-Activated Cyclization. *J. Am. Chem. Soc*. **2016**, *138*, 5218-5221.

[4] Wu, S.-Z.; Wu, X.-Y.; Fu, C.-L.; Ma, S.-M. Rhodium(III)-Catalyzed C–H Functionalization in Water for Isoindolin-1-one Synthesis. *Org. Lett.* **2018**, *20*, 2831-2834.

[5] Zhang, L.-B.; Hao, X.-Q.; Liu, Z.-J.; Zheng, X.-X.; Zhang, S.-K.; Niu, J.-L.; Song, M.-P. Cobalt(II)-Catalyzed C$_{sp2}$-H Alkynylation/Annulation with Terminal Alkynes: Selective Access to 3-Methyleneisoindolin-1-one. *Angew. Chem. Int. Ed.* **2015**, *54*, 10012–10015.

[6] (a) Li, Y.; Li, J.-H. Decarbonylative Formation of Homoallyl Radical Capable of Annulation with *N*-Arylpropiolamides via Aldehyde Auto-oxidation. *Org. Lett*. **2018**, *20*, 5323–5325; (b) Tan, F.-L.; Hu, M.; Song, R.-J.; Li, J. H. Metal-Free Annulation Cascades of 1,7-Enynes Using Di-tert-butyl Peroxide as the Methyl Source towards the Synthesis of Polyheterocyclic Scaffolds. *Adv. Synth. Catal.* **2017**, *359*, 3602-3610; (c) Niu, Z.-J.; Li, L.-H.; Liu, X.-Y.; Liang, Y.-M. Transition-Metal-Free Alkylation/Arylation of Benzoxazole via Tf$_2$O-Activated-Amide. *Adv. Synth. Catal.* **2019**, *361*, 5217 –5222; (d) Li, L.-H.; Niu, Z.-J.; Li, Y.-X.; Liang, Y.-M. Transition-Metal-Free Multinitrogenation of Amides by C–C Bond Cleavage: a new Approach to Tetrazoles. *Chem. Commun.* **2018**, *54*, 11148-11151; (e) Kuang, Z.; Yang, K.; Zhou, Y.; Song, Q. Base-Promoted Domino-Borylation-Protodeboronation Strategy. *Chem. Commun.* **2020**, *56*, 6469-6479; (f) Zhang, J.-J.; Cheng, Y.-B.; Duan, X.-H. Metal-Free Oxidative Decarboxylative Acylation/Ring Expansion of Vinylcyclobutanols with α-Keto Acids by Visible Light Photoredox Catalysis. *Chin. J. Chem.* **2017**, *35*, 311-315; (g) Tang, B.-Z.; Li, J.-Z.; Zhang, A.-W.; Hao, W.-J.; Tu, S.-J.; Jiang, B. Merging [2+2] Cycloaddition with 1,6-/1,4-Aza-Binucleophilic Additions toward Unprecedented Indazole-Containing Polycycles. *Adv. Synth. Catal.* **2019**, *361*, 3394 –3402; (h) Zhang, Z.; Zhu, C. -J.; Miao, M.; Han, J. -L.; Ju, T.; Song, L.; Ye, J. -H.; Li, J.; Yu, D. -G. Lactonization of C(sp^2)—H Bonds in Enamides with CO$_2$. *Chin. J. Chem.* **2018**, *36*, 430-436.

[7] Zhao, W.-X.; Sun, J.-W. Triflimide (HNTf$_2$) in Organic Synthesis. *Chem. Rev*. **2018**, *118*, 10349-10392.

[8] (a) Mendoza, O.; Rossey, G.; Ghosez, L. Brönsted Acid-Catalyzed Synthesis of Diarylmethanes under Non-Genotoxic Conditions. *Tetrahedron Lett*. **2011**, *52*, 2235−2239; (b) Nomiyama, S.; Tsuchimoto,

T. Metal-Free Regioselective β-Alkylation of Pyrroles with Carbonyl Compounds and Hydrosilanes: Use of a Brønsted Acid as a Catalyst. *Adv. Synth. Catal.* **2014**, *356*, 3881−3891; (c) Liu, M.-W.; Zhang, J.-L.; Zhou, H.; Yang, H.-M.; Xia, C.-G.; Jiang, G.-X. Efficient Hydroarylation and Hydroalkenylation of Vinylarenes by Brønsted Acid Catalysis. *RSC Adv.* **2016**, *6*, 76780−76784; (d) Reddel, J. C. T.; Wang,W.; Koukounas, K.; Thomson, R. J. Triflimide-Catalyzed Allylsilane Annulations of Benzylic Alcohols for the Divergent Synthesis of Indanes and Tetralins. *Chem. Sci.* **2017**, *8*, 2156−2160.

[9] (a) Brady, P. B.; Yamamoto, H. Rapid and Stereochemically Flexible Synthesis of Polypropionates: Super-Silyl-Governed Aldol Cascades. *Angew. Chem. Int. Ed.* **2012**, *51*, 1942−1946; (b) Izumiseki, A.; Yamamoto, H. Intermolecular/Intramolecular Sequential Aldol Reaction. *J. Am. Chem. Soc.* **2014**, *136*, 1308−1311.

[10] (a) Zhao, W.-X.; Wang, Z.-B.; Sun, J.-W. Synthesis of Eight-Membered Lactones: Intermolecular [6+2] Cyclization of Amphoteric Molecules with Siloxy Alkynes. *Angew. Chem. Int. Ed.* **2012**, *51*, 6209–6213; (b) Zhao, W.-X.; Qian, H.; Li, Z.-G.; Sun, J.-W. Catalytic Ring Expansion of Cyclic Hemiaminals for the Synthesis of Medium-Ring Lactams. *Angew. Chem. Int. Ed.* **2015**, *54*, 10005–10008; (c) Wang, Y.; Song, L.-J.; Zhang, X.-H.; Sun, J.-W. Metal-Free [2+2+2] Cycloaddition of Ynamides and Nitriles: Mild and Regioselective Synthesis of Fully Substituted Pyridines. *Angew. Chem. Int. Ed.* **2016**, *55*, 9704–9708; (d) Zhang, Y.-S.; Hsung, R.-P.; Zhang, X.-J.; Huang, J.; Slafer, B. W.; Davis, A. Brønsted Acid-Catalyzed Highly Stereoselective Arene-Ynamide Cyclizations. A Novel Keteniminium Pictet−Spengler Cyclization in Total Syntheses of (±)-Desbromoarborescidines A and C. *Org. Lett.* **2005**, *7*, 1047.

[11] (a) Zhang, Y.-Q.; Zhu, X.-Q.; Chen, Y.-B.; Tan, T.-D.; Yang, M.-Y.; Ye, L. -W. Synthesis of Isothiochroman-3-ones via Metal-Free Oxidative Cyclization of Alkynyl Thioethers. *Org. Lett.* **2018**, *20*, 7721-7725; (b) Zhang, Y.-Q.; Zhu, X.-Q.; Xu, Y.; Bu, H.-Z.; Wang, J.-L.; Zhai, T.-Y.; Zhou, J.-M.; Ye, L.-W. Synthesis of Functionalized 3-Isochromanones via Metal-Free Intramolecular Alkoxylation-Initiated Cascade Cyclization. *Green Chem.* **2019**, *21*, 3023-3028; (c) Li, L.; Zhu, X.-Q.; Zhang, Y.-Q.; Bu, H.-Z.; Yuan, P.; Chen, J.; Su, J.-Y.; Deng, X.-M.; Ye, L.-W. Metal-Free Alkene Carbooxygenation following Tandem Intramolecular Alkoxylation/Claisen Rearrangement: Stereocontrolled Access to Bridged [4.2.1] Lactones. *Chem. Sci.* **2019**, *10*, 3123–3129; (d) Zhou, B.; Zhang, Y.-Q.; Zhang, K.-R.; Yang, Y.-M.; Chen, Y.-B.; Li, Y.; Peng, Q.; Zhu, -F.; Zhou, Q.-L.; Ye, L.-W. Stereoselective Synthesis of Medium Lactams Enabled by Metal-Free Hydroalkoxylation/Stereospecific [1,3]-Rearrangement. *Nat. Commun.* **2019**, *10*, 3234; (e) Bu, H.-Z.; Li, H.-H.; Luo, W.-F.; Luo, C.; Qian, P.-C.; Ye, L.-W. Synthesis of 2H-Chromenes via Unexpected [4 + 2] Annulation of Alkynyl Thioethers with o-Hydroxybenzyl Alcohols. *Org. Lett.* **2020**, *22*, 648−652.

[12] (a) Li, M.; Wang, J.-H.; Li, W.; Wen, L.-R.; Metal-Free Direct Construction of 2-(Oxazol-5-yl)phenols from *N*-Phenoxyamides and Alkynylbenziodoxolones via Sequential [3,3]-Rearrangement/Cyclization. *Org. Lett.* **2018**, *20*, 7694-7698; (b) Guo, W.-S.; Gong, H.; Zhang, Y.-A.; Wen, L.-R.; Li, M. Fast Construction of 1,3-Benzothiazepines by Direct Intramolecular Dehydrogenative C–S Bond Formation of Thioamides under Metal-Free Conditions. *Org. Lett.* **2018**, *20*, 6394-6397; (c) Wen, L.-R.; Sun, Y.-X.; Zhang, J.-W.; Guo, W.-S.; Li, M. Catalyst- and Solvent-Free Bisphosphinylation of Isothiocyanates: A Practical Method for the Synthesis of Bisphosphinoylaminomethanes. *Green Chem.* **2018**, *20*, 125-129; (d) Zhang, L.-B.; Geng, R.-S.; Wang, Z.-C.; Ren, G.-Y.; Wen, L.-R.; Li, M. Electrochemical Intramolecular C–H/N–H Functionalization for the Synthesis of Isoxazolidine-Fused Isoquinolin-1(2H)-ones. *Green Chem.* **2020**, *22*, 16-21; (e) Wen, L.-R.; Ren, G.-Y.; Geng, R.-S.; Zhang, L.-B.; Li, M. Fast Construction of Isoquinolin-1(2H)-ones by Direct Intramolecular C–H/N–H Functionalization under Metal-Free Conditions. *Org. Biomol. Chem.* **2020**, *18*, 225-229.

[13] Yoakim, C.; Malenfant, E.; Thavonekham, B.; Ogilvie, W.; Deziel, R. *U.S. Patent Appl. Publ. U.S.* 2,004,106,791, **2004**.

[14] Japtap, P.; Southan, G.; Salzman, A.; Szabo, C.; Ram, S. *PCT Int. Appl.* WO2001077075, **2001**.

[15] (a) Aihara, Y.; Chatani, N. Ruthenium-Catalyzed Direct Arylation of C–H Bonds in Aromatic Amides Containing a Bidentate Directing Group: Significant Electronic Effects on Arylation. *Chem. Sci.* **2013**, *4*, 664-670; (b) Mo, J.; Müller, T.; Oliveira, J.-C.; Demeshko, S.; Meyer, F.; Ackermann, L. Iron-Catalyzed C−H Activation with Propargyl Acetates: Mechanistic Insights into Iron(II) by Experiment, Kinetics, Mössbauer Spectroscopy, and Computation. *Angew. Chem. Int. Ed.* **2019**, *58*, 12874-12878.

[16] [a] Huo, Z.; Gridnev, I. D.; Yamamoto, Y. A Method for the Synthesis of Substituted Quinolines via Electrophilic Cyclization of 1-Azido-2-(2-propynyl)benzene. *J. Org. Chem*. **2010**, *75*, 1266-1270; (b) Kanyiva, K. S.; Hamada, D.; Makino, S.; Takano, H.; Shibata, T. α-Amino Acid Sulfonamides as Versatile Sulfonylation Reagents:Silver-Catalyzed Synthesis of Coumarins and Oxindoles by Radical Cyclization. *Eur. J. Org. Chem*. **2018**, *43*, 5905–5909; (c) Zheng, D.; Yu, J.; Wu, J. Generation of Sulfonyl Radicals from Aryldiazonium Tetrafluoroborates and Sulfur Dioxide: The Synthesis of 3-Sulfonated Coumarins. *Angew. Chem. Int. Ed*. **2016**, *55*, 11925-11929.

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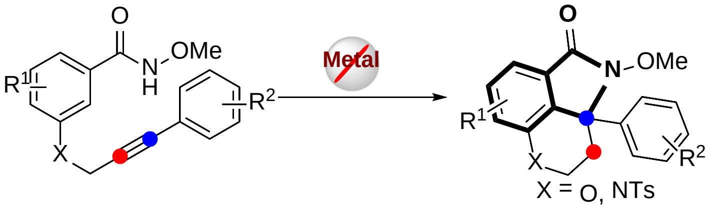
Metal-free Catalyzed Cyclization of *N*-methoxybenzamides to Construct Quaternary Carbon-Containing Isoindolinones



- metal-free catalysis
- 100% atomic economy
- gram-scale synthesis
- construction of quartemary carbon
- broad substrate scope
- DFT calculations

Through the intramolecular cyclization of *N*-methoxybenzamides, a simple and efficient method for constructing valuable isoindolinones under metal-free conditions was developed. The reaction was featured by employing low-cost catalyst, simple operation, 100% atomic economy and excellent regioselectivity. Moreover, a detailed computational study on the reaction system has been performed to clarify the mechanism. This protocol tolerated a variety of functional groups and provided a metal-free protocol for the synthesis of chromane- or tetrahydroquinoline-fused isoindolinones in good yields.

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