Check for updates

ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: J. Liu, H. Fang, R. Cheng, Z. Wang, Y. Yang and J. You, *Chem. Commun.*, 2019, DOI: 10.1039/C9CC03400E.

This is an Accepted Manuscript, which has been through the Royal Society of Chemistry peer review process and has been accepted for publication.

Accepted Manuscripts are published online shortly after acceptance, before technical editing, formatting and proof reading. Using this free service, authors can make their results available to the community, in citable form, before we publish the edited article. We will replace this Accepted Manuscript with the edited and formatted Advance Article as soon as it is available.

You can find more information about Accepted Manuscripts in the author guidelines.

Please note that technical editing may introduce minor changes to the text and/or graphics, which may alter content. The journal's standard Terms & Conditions and the ethical guidelines, outlined in our author and reviewer resource centre, still apply. In no event shall the Royal Society of Chemistry be held responsible for any errors or omissions in this Accepted Manuscript or any consequences arising from the use of any information it contains.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

Please do not adjust margins

ROYAL SOCIETY OF CHEMISTRY View Article Online
DOI: 10.1039/C9CC03400E

Journal Name

COMMUNICATION

Cascade intramolecular imidoylation and C–H activation/annulation of benzimidoyl chlorides with alkynes: one-pot synthesis of 7*H*-dibenzo[*de*,*h*]quinoline analogues

Received 00th January 20xx,
Accepted 00th January 20xx

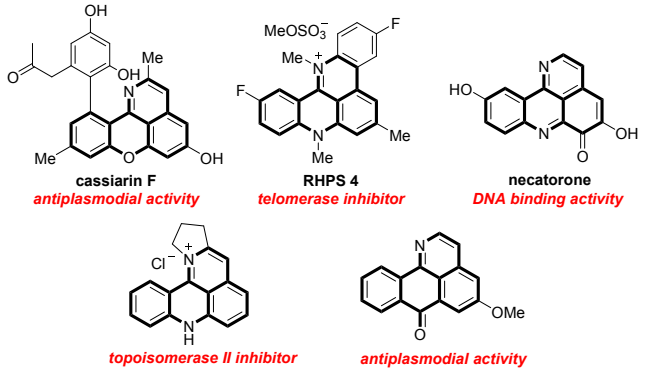
DOI: 10.1039/x0xx00000x

www.rsc.org/

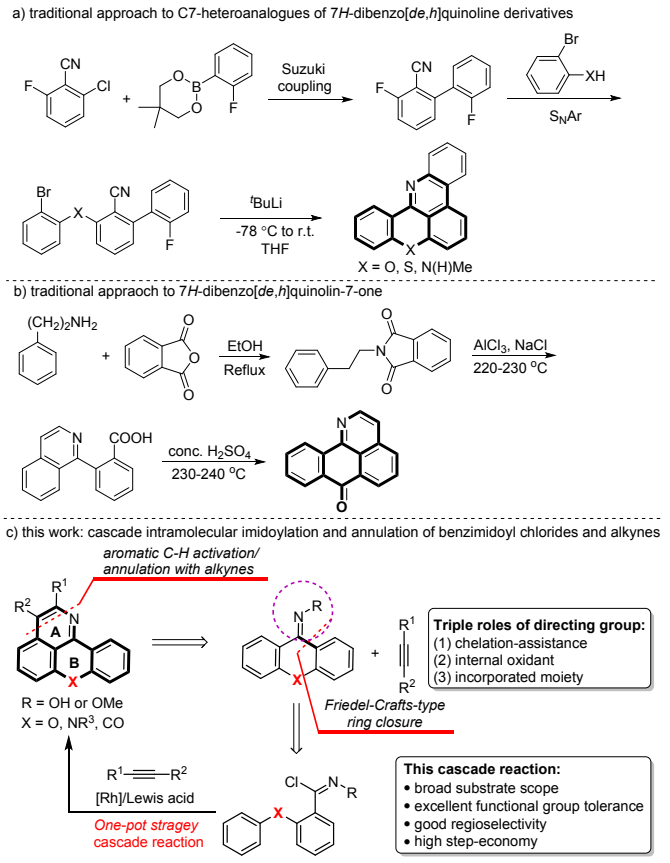
Jiao Liu, Hao Fang, Rui Cheng, Zhishuo Wang, Yudong Yang,* and Jingsong You*

Reported herein is a cascade Lewis acid-promoted intramolecular Friedel–Crafts-type imidoylation and Rh(III)-catalyzed C–H activation/annulation of benzimidoyl chlorides and alkynes, providing a general and concise one-pot approach to 7*H*-dibenzo[*de*,*h*]quinoline analogues. This divergent approach is based on a convergent retrosynthetic disconnection strategy.

The 7*H*-dibenzo[*de*,*h*]quinoline analogues, such as chromeno[2,3,4-*ij*]isoquinolines, 7-methyl-7*H*-pyrido[4,3,2-*kl*]acridines and 7*H*-dibenzo[*de*,*h*]quinolin-7-ones (oxoisoaporphines), widely exist in natural products and pharmaceuticals. Molecules containing these motifs often exhibit a broad spectrum of biological activities such as antiplasmodial, antifungal, antitumor and DNA binding activities (Scheme 1).[1] Conventional approaches to 7*H*-dibenzo[*de*,*h*]quinoline analogues mainly depend on sequential Suzuki cross-coupling/nucleophilic aromatic substitution/anionic cascade ring-closing reaction (for C7-heteroanalogues of 7*H*-dibenzo[*de*,*h*]quinolines, Scheme 2a),[2] and successive thermal cyclization of phthalimide derivatives at an extremely high temperature (for 7*H*-dibenzo[*de*,*h*]quinolin-7-ones, Scheme 2b).[1g,1j,3] Despite the significance of these methods, they typically suffer from tedious synthetic routes, low atom-/step-economy, poor functional group tolerance and harsh reaction



Scheme 1. Selected examples of 7*H*-dibenzo[*de*,*h*]quinoline derivatives and their heteroanalogues



Scheme 2. Synthesis of 7*H*-dibenzo[*de*,*h*]quinoline derivatives and their heteroanalogues

Key Laboratory of Green Chemistry and Technology of Ministry of Education, College of Chemistry, Sichuan University, 29 Wangjiang Road, Chengdu 610064, P. R. China. Email: yangyudong@scu.edu.cn; E-mail: jsyou@scu.edu.cn.

Electronic Supplementary Information (ESI) available: Detailed experimental procedures, characterization data, X-ray crystallographic data (CCDC 1899576 (**3b**), 1913390 (**3d**), 1899575 (**3e**), 1899578 (**3f**), 1899572 (**5g**), 1899579 (**5h**) and 1899574 (**7d**)). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/x0xx00000x

Published on 29 May 2019. Downloaded by Boston University on 5/29/2019 2:51:10 AM.

ChemComm Accepted Manuscript

Please do not adjust margins

View Article Online DOI: 10.1039/C9CC03400E

Published on 29 May 2019. Downloaded by Boston University on 5/29/2019 2:51:10 AM.

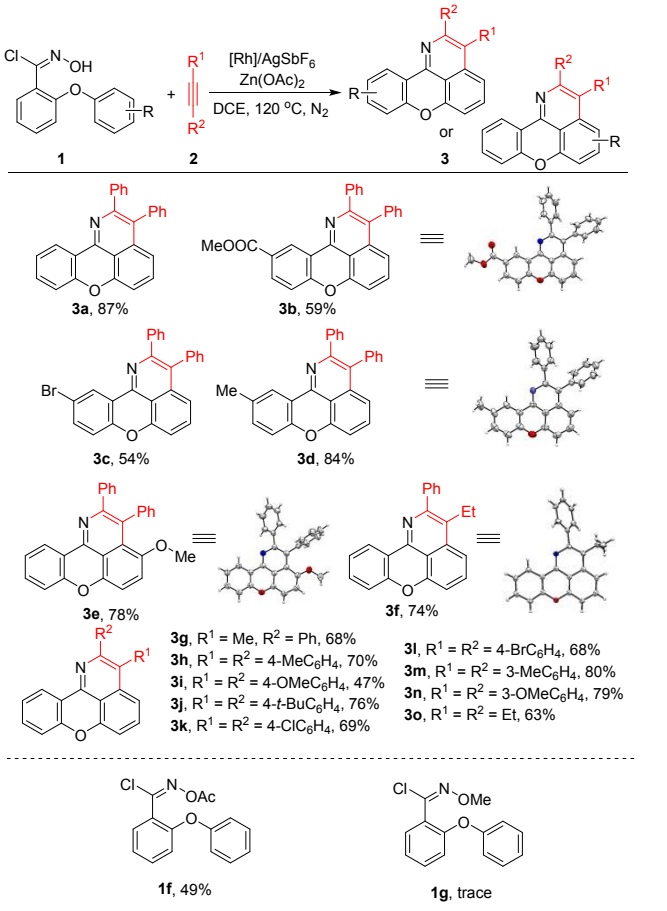
conditions. Therefore, the development of a more general, concise and efficient method for the synthesis of 7*H*-dibenzo[*de*,*h*]quinoline analogues is still in high demand.

In the past decade, transition metal-catalyzed annulation of aromatic compounds with alkynes through chelation-assisted C–H activation has emerged as one of the most straightforward and efficient methods to construct polycyclic (hetero)aromatic compounds.[4,5] In particular, the redox-neutral C–H activation/annulation reaction is highly attractive owing to the obviation of external metal oxidants.[6] Moreover, this strategy may provide a completely different retrosynthetic opportunity for the synthesis of complex molecules. Indeed, the retrosynthetic analysis of 7*H*-dibenzo[*de*,*h*]quinoline derivatives and their C7-aza/-oxa analogues suggests that the pyridyl ring (ring A) could be constructed by the annulation of an oxime with an alkyne component. The ring B could be accessed via an intramolecular Friedel–Crafts-type imidoylation (Scheme 2c). Based on this convergent retrosynthetic logic, herein we disclose a cascade Lewis acid-promoted intramolecular Friedel–Crafts-type imidoylation and Rh(III)-catalyzed C–H activation/annulation using benzimidoyl chlorides and alkynes as the starting materials, providing a divergent synthetic short-cut to 7*H*-dibenzo[*de*,*h*]quinoline deriv-atives and their C7-aza/-oxa analogues. This reaction features a broad substrate scope, excellent functional group tolerance, good regioselectivity and high step-economy. Notably, the directing group in this reaction plays triple roles as a chelation-assisted group, internal oxidant and incorporated moiety in the final product.

With the retroanalysis in mind, *N*-hydroxy-2-phenoxybenzimidoyl chloride **1a** was initially synthesized and selected as the model substrate (Table S1). Reaction of **1a** (0.10 mmol) with diphenylacetylene **2a** (0.15 mmol) gave rise to chromeno[2,3,4-*ij*]isoquinoline **3a** in 35% yield in the presence of $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$(20 mol %), PivOH (2.0 equiv) and $Zn(OAc)_2{\cdot}2H_2O$ (1.0 equiv) in DCE at 140 °C under nitrogen atmosphere for 24 h (Table S1, entry 1). Other Lewis acids such as $Zn(OTf)_2$, $Mn(OAc)_2$, $Ni(OAc)_2{\cdot}4H_2O$, $Mg(OAc)_2{\cdot}2H_2O$ and bases such as LiOAc and CsOAc were proven to be less efficient in this transformation (Table S1, entries 2-7). Lowering the reaction temperature to 120 °C could slightly improve the yield to 40% (Table S1, entry 8). Further lowering the temperature led to a diminished yield (Table S1, entries 9 and 10). An improved yield of 67% was observed in the absence of PivOH, indicating the detrimental effect of PivOH to this reaction (Table S1, entry 11). Adjusting the stoichiometric ratio of **1a**:**2a** to 1.5:1 led to 87% yield (Table S1, entry 13). In addition, no desired product was detected in the absence of either $[Cp^*RhCl_2]_2$ or $AgSbF_6$, suggesting the essential role of these two additives (Table S1, entries 14 and 15). Only trace amounts of the desired product was detected when $[Cp^*Co(CO)I_2]_2$ was employed as the catalyst (Table S1, entry 17). Finally, the optimal reaction conditions were assigned as follow: $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), and $Zn(OAc)_2$ (1.0 equiv) in DCE at 120 °C under N_2 for 24 h.

With the optimized reaction conditions in hand, we investigated the scope of substrates (Table 1). A variety of *N*-hydroxy-2-aryloxybenzimidoyl chlorides **1** could smoothly react with diphenyl alkyne **2a** under the standard condition (**3a**-**3e**). Common functional groups including -COOMe, -Br, -Me and -OMe were tolerated (**3b**-**3e**). Typically, the substrates with the electron-donating group on the phenyl ring gave higher yields than their analogues with the electron-withdrawing group (**3b** and **3c** vs **3d** and **3e**). Notably, the electronic nature of substituents on phenyl ring had a significant influence on the regioselectivity of C−H activation. The relatively more electronic-rich aryl ring typically preferred to undergo the annulation with an alkyne, implying that an electrophilic aromatic substitution (S_EAr) process might be involved in the C−H rhodation step (**3b**, **3c** and **3e**).[7] However, an exception was found in the case of product **3d**, probably owing to the large steric effect of -Me. The Aryl alkyl, dialkyl and diaryl acetylenes with various electronically different substituents were also suitable substrates (**3f**-**3o**). When aryl alkyl alkynes were subjected to the reaction, the C−N bond formation tended to take place at the acetylene carbon neighboring to the aryl substituent (**3f** and **3g**). In addition, the X-ray single crystal diffraction of **3b**, **3d**, **3e** and **3f** further confirmed the product structures. It is worth noting that only H_2O and HCl were produced as the by-products in this reaction. Notably, *N*-acetoxy-2-phenoxybenzimidoyl chloride **1f** was also proved to be an effective substrate, giving the desired product **3a** in 49% yield. However, the attempt with a *N*-methoxy-analogue (**1g**) was failed. Additionally, the reaction of **1a** and phenylacetylene failed to deliver the desired product.

Table 1. Scope of *N*-hydroxy-2-phenoxybenzimidoyl chlorides and alkynes[a]



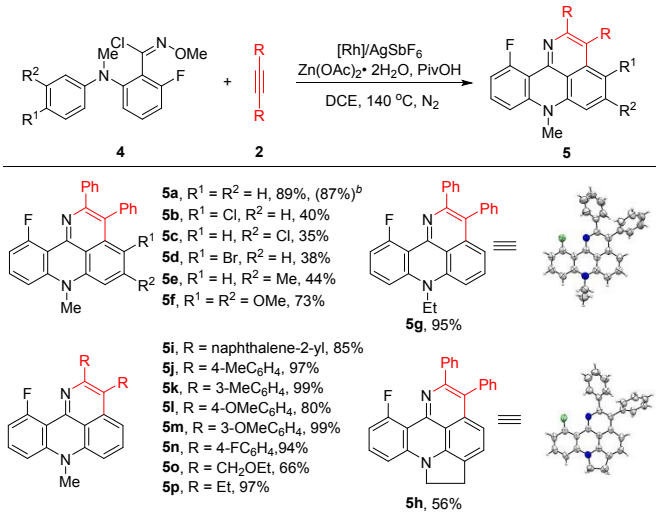
[a] Reaction condition **A**: **1** (0.15 mmol), **2** (0.10 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), $Zn(OAc)_2$ (1.0 equiv) and DCE (2 mL) at 120 °C under N_2 for 24 h. Isolated yield. DCE = 1,2-dichloroethane.

ChemComm Accepted Manuscript

This journal is © The Royal Society of Chemistry 20xx

View Article Online
DOI: 10.1039/C9CC03400E

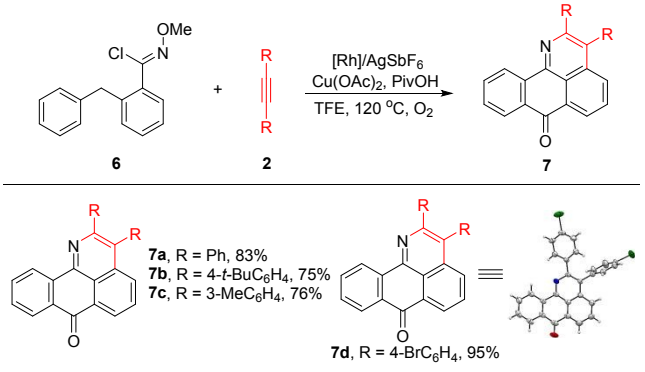
Table 2. Scope of *N*-methoxy-2-(methyl(phenyl)amino)benzimidoyl chlorides and alkynes[a]



[a] Reaction condition **B**: **4** (0.15 mmol), **2** (0.1 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), $Zn(OAc)_2{\cdot}2H_2O$ (0.1 mmol), PivOH (0.2 mmol) and DCE (2 mL) at 140 °C under N_2 for 12 h. Isolated yield. [b] 1 mmol scale. DCE = 1,2-dichloroethane.

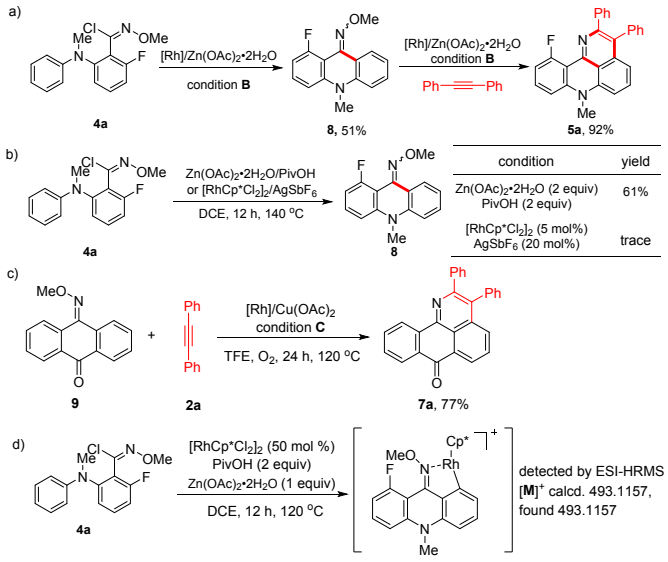
Encouraged by these results, the cascade reaction for the synthesis of pyrido[4,3,2-*kl*]acridine derivatives was carried out (Table 2). Under a slightly modified reaction condition, *N*-methoxy benzimidoyl chlorines **4** could smoothly react with acetylenes **2**, giving the desired products **5** in moderate to excellent yields. This reaction exhibited a broad substrate scope for both *N*-methoxy benzimidoyl chlorines and acetylenes (**5a**-**5p**). Similarly, the electron-donating substituents on the phenyl ring of 4 showed a positive effect on the yield (**5f** vs **5b**-**5e**). However, terminal alkynes did not work in this reaction, as exemplified by the reaction of **4a** with phenylacetylene.

Table 3. Scope of 2-benzyl-*N*-methoxybenzimidoyl chloride and alkynes[a]



[a] Reaction condition **C**: **2** (0.1 mmol), **6** (0.15 mmol), $[Cp^*RhCl_2]_2$ (5 mol %), $AgSbF_6$ (20 mol %), $Cu(OAc)_2$ (0.3 mmol), PivOH (0.2 mmol) and TFE (2 mL) at 120 °C under O_2 for 24 h. Isolated yield. TFE = 2,2,2-trifluoroethanol.

The reaction of 2-benzoyl-*N*-methoxybenzimidoyl chloride and diphenyl acetylene under the reaction conditions **A** and **B** were conducted for the synthesis of oxoisoaporphine derivative. However, no desired product was detected perhaps because the strong electron-withdrawing effect of the carbonyl group inhibits the intramolecular Friedel–Crafts-type ring closure. To our delight, the cascade annulation of 2-benzyl-*N*-methoxybenzimidoyl chloride **6** and alkynes **2** could furnish the oxoisoaporphine derivatives **7** in good to excellent yields in the presence of a $Cu(OAc)_2/O_2$ oxidative system (Table 3).



Scheme 3. Mechanistic investigation

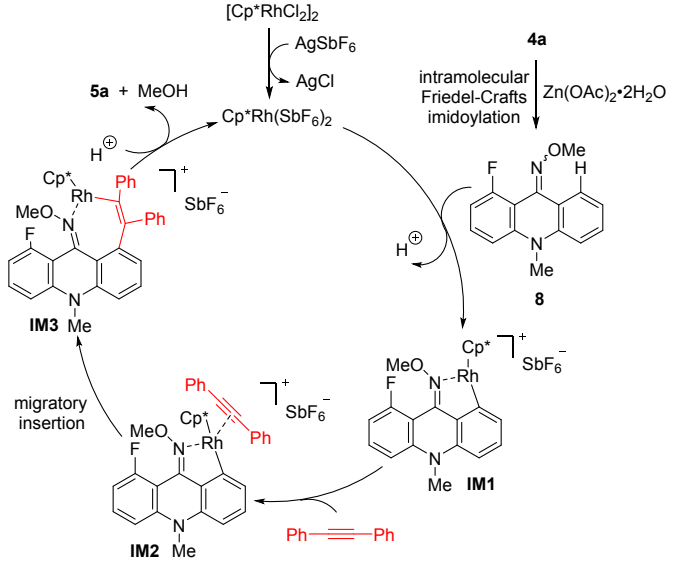
To gain some insights into the reaction mechanism, several control experiments were conducted. First, the reaction of benzimidoyl chloride **4a** in the absence of acetylene under the standard condition B gave **8** in 51% yield. Further reaction of **8** and diphenyl acetylene **1a** could deliver **5a** in 92% yield (Scheme 3a). These results suggested an intramolecular Friedel–Crafts imidoylation/C–H activation/annulatuion sequence for this cascade reaction. In addition, the imidoylation could proceed well in the absence of $[Cp^*RhCl_2]_2$ and $AgSbF_6$ (Scheme 3b). However, only trace amounts of the desired product **8** was detected in the absence of $Zn(OAc)_2{\cdot}2H_2O$ (Scheme 3b). These results indicated that the Friedel–Crafts imidoylation was mainly mediated by $Zn(OAc)_2$ rather than rhodium or silver species. Additionally, treatment of oxime **9** with diphenyl alkyne **2a** under the condition **C** provided the corresponding annulated product **7a** in 77% yield (Scheme 3c). This observation implied that oxime **9** might be an intermediate in the cascade annulation of **6** and alkynes **2**. Considering that 2-benzoyl-*N*-methoxybenzimidoyl chloride is not an effective substrate in this cascade reaction, the oxidation of the methylene group might take place after the intramolecular imidoylation but before the annulation with alkynes. Finally, in the reaction mixture of **4a** with stoichiometric amounts of $[Cp^*RhCl_2]_2$ (condition **B**, 120 °C), a cationic rhodacycle complex was detected by ESI-HRMS ($[\mathbf{M}]^+$ calcd. 493.1157, found 493.1157), suggesting a C–H activation process was involved (Scheme 3d).

Published on 29 May 2019. Downloaded by Boston University on 5/29/2019 2:51:10 AM.
ChemComm Accepted Manuscript

View Article Online
DOI: 10.1039/C9CC02400E

Published on 29 May 2019. Downloaded by Boston University on 5/29/2019 2:51:10 AM.

Based on the above observations and previous reports[8], a tentative reaction mechanism is proposed (Scheme 4). First, a cationic rhodium species is produced by chloride abstraction with $AgSbF_6$. Then, an oxime-directed ortho C–H rhodation of **8**, which is generated by $Zn(OAc)_2$-mediated intramolecular Friedel–Crafts-type imidoylation of *N*-methoxy benzimidoyl chlorines **4a**, delivers a five-membered rhodacycle species **IM1**. Following migratory insertion of the alkyne **2a** delivers rhodacycle **IM3**, which then undergoes a redox-neutral process to furnish the desired product **5a** with the release of rhodium catalyst for the next catalytic cycle.



Scheme 4. Plausible mechanistic pathway.

In summary, we have developed a general, concise and efficient protocol for the synthesis of 7*H*-dibenzo[*de*,*h*]quinoline analogues via a cascade Lewis acid-promoted intramolecular Friedel–Crafts-type imidoylation and Rh(III)-catalyzed C–H activation/annulation of benzimidoyl chlorides with alkynes. This reaction features a broad substrate scope, good functional group tolerance and excellent regioselectivity, and could enable rapid scaffold diversification. A variety of chromeno[2,3,4-*ij*]isoquinoline, 7-methyl-7*H*-pyrido[4,3,2-*kl*]acridine and 7*H*-dibenzo[*de*,*h*]quinolin-7-one could be obtained in this cascade reaction. Studies on the application of this reaction to the exploitation of bioactive molecules are ongoing in our laboratory.

We thank the National Natural Science Foundation of China (Nos. 21432005 and 21502123) for financial support. We also thank the Open Fund of the Key Laboratory of Functional Molecular Engineering of Guangdong Province (2016kf05, South China University of Technology) and the Comprehensive Training Platform Specialized Laboratory, College of Chemistry, Sichuan University.

Conflicts of interest

There are no conflicts to declare.

Notes and references

1 (*a*) K. M. Marshall and L. R. Barrows, *Nat. Prod. Rep.*, 2004, **21,** 731; (*b*) J. Kaur and P. Singh, *Expert Opin. Ther. Patents*, 2011, **21,** 437; (*c*) J. Stanslas, D. J. Hagan, M. J. Ellis, C. Turner, J. Carmichael, W. Ward, T. R. Hammonds and M. F. G. Stevens, *J. Med. Chem.*, 2000, **43,** 1563; (*d*) L. Bouffier, R. Dinica, J. Debray, P. Dumy and M. Demeunynck, *Bioorg. Med. Chem. Lett.*, 2009, **19,** 4836; (*e*) J. R. De la Fuente, C. Aliaga, C. Poblete, G. Zapata, C. Jullian, C. Saitz, A. Cañete, G. Kciuk, E. Sobarzo-Sanchez and K. J. Bobrowski, *Phys. Chem. A*, 2009, **113,** 7737; (*f*) J. Deguchi, T. Hirahara, S. Oshimi, Y. Hirasawa, W. Ekasari, O. Shirota, T. Honda, and H. Morita, *Org. Lett.*, 2011, **13,** 4344; (*g*) V. Castro-Castillo, C. Suárez-Rozas, A. Pabón, E. G. Pérez, B. K. Cassels and S. Blair, *Bioorg. Med. Chem. Lett.*, 2013, **23,** 327; (*h*) A. R. O. Cousins, D. Ritson, P. Sharma, M. F. G. Stevens, J. E. Moses and M. S Searle, *Chem. Commun.*, 2014, **50,** 15202; (*i*) A. Rizzo, S. Iachettini, P. Zizza, C. Cingolani, M. Porru, S. Artuso, M. Stevens, M. Hummersone, A. Biroccio, E. Salvati and C. Leonetti, *J. Exp. Clin. Cancer Res.*, 2014, **33,** 81; (*j*) Z.-F. Chen, Q.-P. Qin, J.-L. Qin, Y.-C. Liu, K.-B. Huang, Y.-L. Li, T. Meng, G.-H. Zhang, Y. Peng, X.-J. Luo and H. Liang, *J. Med. Chem.*, 2015, **58,** 2159.

2 J. L. Kristensen, P. Vedsø and M. Begtrup, *J. Org. Chem.*, 2003, **68,** 4091.

3 Y.-P. Li, F.-X. Ning, M.-B. Yang, Y.-C. Li, M.-H. Nie, T.-M. Ou, J.-H. Tan, S.-L. Huang, D. Li, L.-Q. Gu and Z.-S. Huang, *Eur. J. Med. Chem.*, 2011, **46,** 1572.

4 (*a*) T. Satoh and M. Miura, *Chem. —Eur. J*. 2010, **16,** 11212; (*b*) P. B. Arockiam, C. Bruneau and P. H. Dixneuf, *Chem. Rev.*, 2012, **112,** 5879; (*c*) Y. Yang, K. Li, Y. Cheng, D. Wan, M. Li and J. You, *Chem. Commun.*, 2016, **52,** 2872; (*d*) M. Gulías and J. L. Mascareñas, *Angew. Chem., Int. Ed.*, 2016, **55,** 11000; (*e*) S. Prakash, R. Kuppusamy and C.-H. Cheng, *ChemCatChem.*, 2018, **10,** 683; (*f*) G. Duarah, P. P. Kaishap, T. Begum and S. Gogoi, *Adv. Synth. Catal.*, 2019, **361,** 654.

5 (*a*) G. Zhang, L. Yang, Y. Wang, Y. Xie and H. Huang, *J. Am. Chem. Soc.*, 2013, **135,** 8850; (*b*) S. Warratz, C. Kornhaaβ, A. Cajaraville, B. Niepötter, D. Stalke and L. Ackermann, *Angew. Chem., Int. Ed.*, 2015, **54,** 5513; (*c*) S. Prakash, K. Muralirajan and C.-H. Cheng, *Angew. Chem., Int. Ed.*, 2016, **55,** 1844; (*d*) X. Xu, H. Zhao, J. Xu, C. Chen, Y. Pan, Z. Luo, Z. Zhang, H. Li and L. Xu, *Org. Lett.*, 2018, **20,** 3843; (*e*) J. Yin and J. You, *Angew. Chem., Int. Ed.*, 2019, **58,** 302; (*f*) A. Obata, A. Sasagawa, K. Yamazaki, Y. Ano and N. Chatani, *Chem. Sci.*, 2019, **10,** 3242.

6 (*a*) J. Mo, L. Wang, Y. Liu and X. Cui, *Synthesis*, 2015, **47,** 439; (*b*) L. Zheng and R. Hua, *Chem. Rec.*, 2018, **18,** 556; (*c*) B. Sun, T. Yoshino, M. Kanai and S. Matsunaga, *Angew. Chem., Int. Ed.*, 2015 ,**54,** 12968; (*d*) Z. Zhou, G. Liu, Y. Chen and X. Lu, *Adv. Synth. Catal.*, 2015, **357,** 2944; (*e*) K.-H. He, W.-D. Zhang, M.-Y. Yang, K.-L. Tang, M. Qu, Y.-S. Ding and Y. Li, *Org. Lett.*, 2016, **18,** 2840; (*f*) A. Lerchen, S. Vásquez-Céspedes and F. Glorius, *Angew. Chem., Int. Ed.*, 2016, **55,** 3208; (*g*) Q. Lu, S. Greßies, S. Cembellín, F. J. R. Klauck, C. G. Daniliuc and F. Glorius, *Angew. Chem., Int. Ed.*, 2017, **56,** 12778; (*h*) Y.-F. Liang, R. Steinbock, A. Münch, D. Stalke and L. Ackermann, *Angew. Chem., Int. Ed.*, 2018, **57,** 5384.

7 (*a*) W. Ma, R. Mei, G. Tenti and L. Ackermann, *Chem. —Eur. J.*, 2014, **20,** 15248; (*b*) E. Tan, O. Quinonero, M. E. Orbe and A. M. Echavarren, *ACS Catal.*, 2018, **8,** 2166; (*c*) Y. Shi, L. Zhang, J. Lan, M. Zhang, F. Zhou, W. Wei and J. You, *Angew. Chem., Int. Ed.*, 2018, **57,** 9108.

8 (*a*) G. Song and X. Li, *Acc. Chem. Res.*, 2015, **48,** 1007; (*b*) N. Guimond, S. I. Gorelsky and K. Fagnou, *J. Am. Chem. Soc.*, 2011, **133,** 6449; (*c*) M. Sen, D. Kalsi and B. Sundararaju, *Chem. —Eur. J.*, 2015, **21,** 15529; (*d*) J. Tang, S. Li, Z. Liu, Y. Zhao, Z. She, V. D. Kadam, G. Gao, J. Lan and J. You, *Org. Lett.*, 2017, **19,** 604.

ChemComm Accepted Manuscript

This journal is © The Royal Society of Chemistry 20xx