Organic & Biomolecular Chemistry

ROYAL SOCIETY OF CHEMISTRY

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2020, **18**, 135

Lewis or Brønsted acid-catalysed reaction of propargylic alcohol-tethered alkylidenecyclopropanes with indoles and pyrroles for the preparation of polycyclic compounds tethered with indole or pyrrole motif†

Hao-Zhao Wei,[a] Liu-Zhu Yu[a] and Min Shi *[a,b]

Received 12th October 2019,
Accepted 21st November 2019

DOI: 10.1039/c9ob02211b

rsc.li/obc

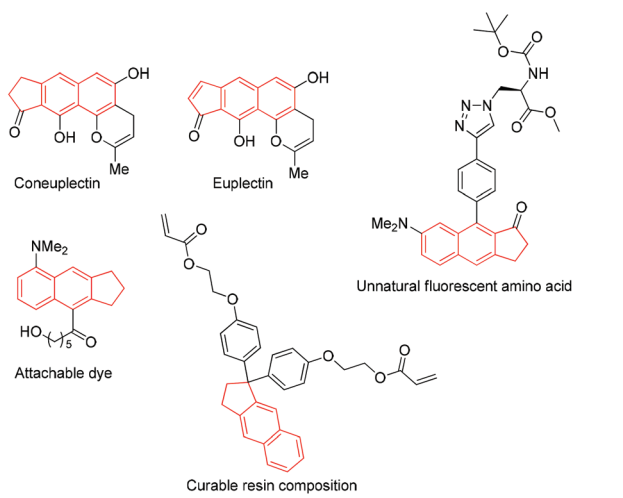
We developed a facile synthetic method to access cyclopenta[*b*]naphthalene derivatives *via* the Lewis or Brønsted acid catalysed cascade nucleophilic addition, electronic cyclization, ring-opening rearrangement of propargylic alcohol-tethered alkylidenecyclopropanes with indole and pyrrole derivatives. The reaction exhibited a broad substrate scope and good functional group tolerance under metal-free conditions, affording the desired products in moderate to good yields.

Introduction

Cyclopenta[*b*]naphthalene structural motifs exist in numerous natural products[1] and functional materials.[2] Besides, naphthalene-based dyes consisting of cyclopenta[*b*]naphthalene and other groups possess desirable photophysical properties such as wavelength-dependent emission with changes in microenvironment polarity, high quantum yield, and decent photostability (Scheme 1).[3]

Indole and its derivatives are extensively distributed in natural products and are general structural motifs in pharmaceuticals.[4] Their different and productive biological activities have resulted in their classification as "privileged" heterocycles in medicinal chemistry.[4a,g,5] Methylenecyclopropanes (MCPs) are a type of highly strained molecule and have been widely applied in organic synthesis,[6] pharmaceutical chemistry,[7] agricultural chemistry,[8] and even materials science.[9] MCPs can undergo an assortment of reactions, which are facilitated owing to the release of the intramolecular strain of its small ring and exocyclic C–C bond. Propargylic alcohols can undergo various cascade processes to furnish structurally attractive carbocycles or heterocycles by forming *in situ* generated allenes. Lewis/Brønsted acid-catalysed nucleophilic substitution of propargylic alcohols is essential in organic synthetic chemistry, which can be converted into diverse acyclic, carbocyclic, and heterocyclic synthetic building blocks.[10] To design a novel cascade reaction under mild conditions, we considered applying indole or pyrrole as a nucleophile to trigger an intermolecular cascade reaction of propargylic alcohol-tethered methylene cyclopropanes.

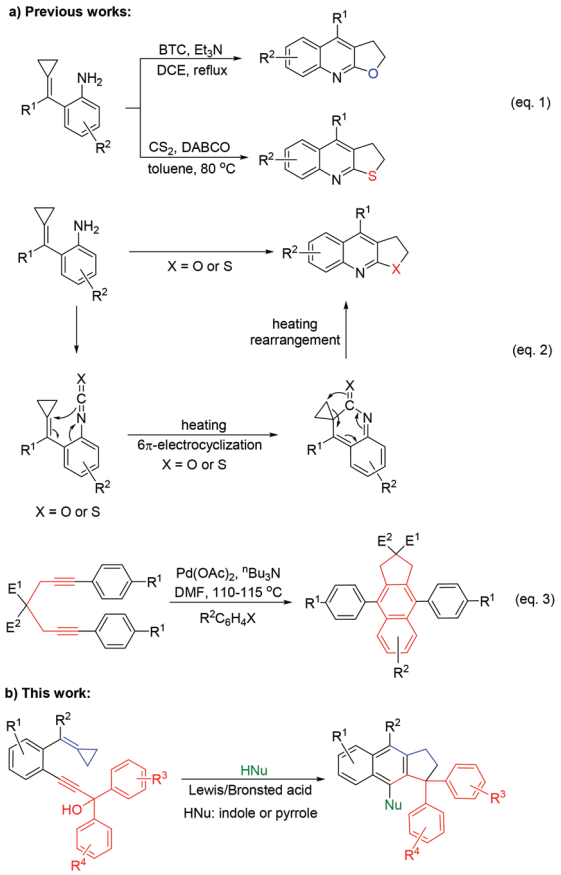
In 2016, our group reported a thermally induced ring-opening and cyclization reaction from *ortho*-aminoaryl-tethered alkylidenecyclopropanes with *in situ* generated isocya-



Scheme 1 Representative examples containing cyclopenta[*b*]naphthalene skeleton.

[a]*Key Laboratory for Advanced Materials and Institute of Fine Chemicals, School of Chemistry & Molecular Engineering, East China University of Science and Technology, 130 Meilong Road, Shanghai 200237, China*
[b]*State Key Laboratory of Organometallic Chemistry, Center for Excellence in Molecular Synthesis, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 345 Ling-Ling Lu, Shanghai, 200032, China. E-mail: mshi@mail.sioc.ac.cn*

†Electronic supplementary information (ESI) available: Detailed experimental procedures and analytical data. CCDC 1584674. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9ob02211b



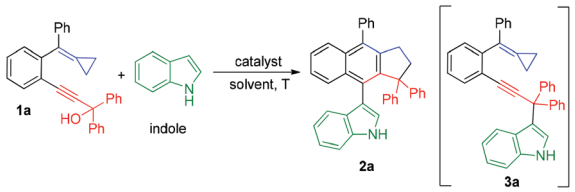
Scheme 2 Previous works and this work.

nates or isothiocyanates to afford furoquinoline and thienoquinoline derivatives (Scheme 2, eqn (1) and (2)).[6g] In 2010, Hu and co-workers reported a method to construct 4,9-diphenyl-2,3-dihydro-1*H*-cyclopenta[*b*]naphthalene derivatives *via* the palladium(0)-catalysed reaction of diynes with aryl halides through C–C coupling and C–H bond activation of the incorporated aryl group (Scheme 2, eqn (3)).[11] Based on these previous findings, herein, we report the Lewis or Brønsted acid catalysed and pronucleophile-involved [3 + 2] cyclization reaction of propargyl alcohol-tethered methylene cyclopropanes with the *in situ* generated allene moiety for the facile synthesis of cyclopenta[*b*]naphthalene derivatives under metal-free conditions.

Results and discussion

We initially investigated the reaction outcome using **1a** as a model substrate in the presence of indole (1.0 equiv.) and found that the desired cyclized product **2a** was obtained in 50% yield accompanied with by-product **3a** at room temperature in acetonitrile using $BF_3{\cdot}OEt_2$ (20 mol%) as the catalyst (Table 1, entry 1). Then, we evaluated different temperatures ranging from 40 °C to 80 °C and identified that room temperature is the most appropriate temperature in acetonitrile for

Table 1 Screening of reaction conditions



Entry[a]	Catalyst	Solvent	*T* [°C]	Yield[b]/**2a** [%]	**2a** : **3a**[e]
1	$BF_3{\cdot}OEt_2$	MeCN	rt	50	1.6 : 1
2	$BF_3{\cdot}OEt_2$	MeCN	40	41	1.6 : 1
3	$BF_3{\cdot}OEt_2$	MeCN	80	32	1.8 : 1
4	$BF_3{\cdot}OEt_2$	EA	rt	43	1.0 : 1
5	$BF_3{\cdot}OEt_2$	PhCl	rt	—	—
6	$BF_3{\cdot}OEt_2$	PhMe	rt	22	1.1 : 1
7	$Sc(OTf)_3$	MeCN	rt	37	1.5 : 1
8	$AgSbF_6$	MeCN	rt	—	—
9	CF_3SO_3H	MeCN	rt	40	1.3 : 1
10	CH_3COOH	MeCN	rt	—	—
11	CF_3COOH	MeCN	rt	55	2.0 : 1
12	CF_3COOH	DMF	rt	—	—
13	CF_3COOH	DMSO	rt	—	—
14	CF_3COOH	PhMe	rt	51	1.2 : 1
15	CF_3COOH	PhCl	rt	63	1.9 : 1
16	CF_3COOH	PhF	rt	50	1.2 : 1
17[c]	CF_3COOH	PhCl	rt	60	1.9 : 1
18[d]	CF_3COOH	PhCl	rt	57	1.4 : 1

[a] Reaction conditions: **1a** (0.10 mmol, 1.0 equiv.), indole (0.10 mmol, 1.0 equiv.), catalyst (20 mol%), solvent (1.0 mL), *T*, for 6 h. [b] ^{1}H NMR yield using 1,3,5-trimethoxybenzene as an internal standard. [c] Reaction conditions: **1a** (0.40 mmol, 0.2 equiv.), indole (0.20 mmol, 1.0 equiv.), catalyst (20 mol%), solvent (2.0 mL). [d] Reaction conditions: **1a** (0.20 mmol, 1.0 equiv.), indole (0.20 mmol, 1.0 equiv.), catalyst (20 mol%), solvent (2.0 mL), isolated yield. [e] The ratio of **2a** and **3a** was determined by ^{1}H NMR spectroscopic data.

this reaction in the presence of $BF_3{\cdot}OEt_2$ (Table 1, entries 2 and 3). The examination of solvent effects revealed that acetonitrile is the most suitable solvent for this reaction with $BF_3{\cdot}OEt_2$ as the catalyst at room temperature (Table 1, entries 4–6). Several other Lewis acids such as $Sc(OTf)_3$ and $AgSbF_6$ were tested in acetonitrile, but no better result was obtained (Table 1, entries 7 and 8). Next, Brønsted acids such as trifluoromethylsulfonic acid (TfOH), acetic acid (CH_3CO_2H) and trifluoroacetic acid (CF_3COOH) were selected as the catalyst for this reaction and we identified that the use of CF_3COOH as the catalyst gave **2a** in 55% yield along with **3a** as the by-product (Table 1, entries 9–11). It should be noted that the acids used as catalysts should have enough acidity to remove the hydroxyl group to generate the carbocationic intermediate, but too strong Brønsted acid such as TfOH can decompose the MCP group, which will cause the production of **2a** in lower yield. After screening solvents in the presence of CF_3COOH at room temperature, we found that chlorobenzene was the solvent of choice, giving **2a** in 63% yield (Table 1, entries 12–16). Using 2.0 equiv. of **1a** to react with 1.0 equiv. of indole or carrying out the reaction in a diluted solution in 2.0 mL of MeCN did not further improve the yield of **2a** (Table 1, entries 17 and 18) (for more details on the screening

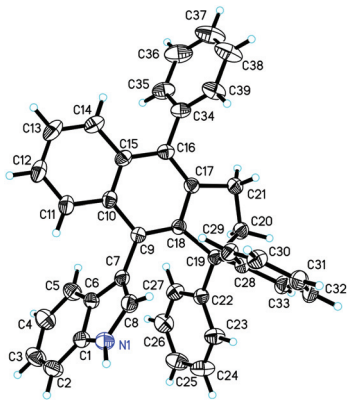
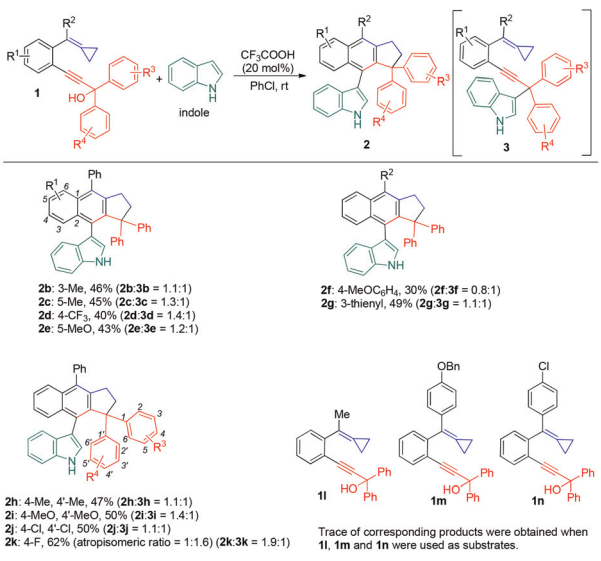


Fig. 1 X-ray structures of **2a**.

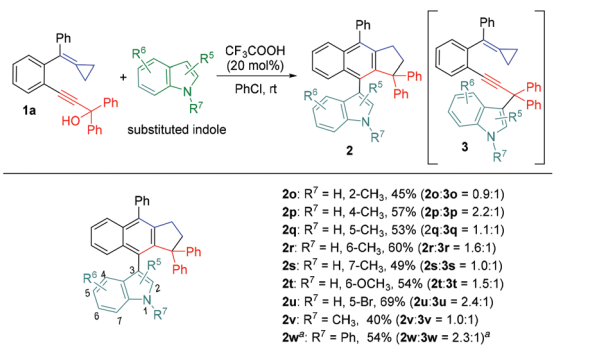
of reaction conditions including other Brønsted acids, see Tables S1 and S2 in the ESI†). It should be mentioned here that the production of **3a** could not be avoided due to the two competitive addition reactions, which produced **2a** and **3a** (see Scheme 6 for the reaction mechanism).[12] The structure of **2a** was unambiguously established by X-ray diffraction. The ORTEP drawing of **2a** is shown Fig. 1, and the corresponding CIF data is presented in the ESI.†

With the optimized reaction condition in hand, we next surveyed a range of substrates for this reaction. We first turned our attention toward the scope of the catalytic cascade cyclization of propargylic alcohol-tethered alkylidenecyclopropanes (**1b–1n**) with indole as the nucleophile, and the results are summarized in Scheme 3. The R^1 substituent could be electron-donating and electron-withdrawing at different positions, affording the desired products **2b–2e** in moderate yields ranging from 40% to 46%. When R^2 was a methoxyphenyl group or a heteroaromatic ring, the reaction proceeded smoothly, producing the desired products **2f** and **2g** in 30% and 49% yields, respectively. The electron-donating and electron-withdrawing substituent could be also introduced at the benzene ring in the propargylic alcohol moiety, giving the desired products **2h–2k** in moderate to good yields. It should be noted that **2k** was presented as two atropisomers owing to the rotation obstruction of the C–C bond connecting the indole moiety to the cyclopenta[*b*]naphthalene motif. The reaction was sensitive to the R^2 group in the presence of indole (Scheme 3). When substrates **1l** (R^2 = Me) and **1n** (R^2 = 4-ClC_6H_4) were applied for the reaction, traces of the corresponding cyclized products were obtained because these groups with a lower electron density compared to the phenyl group would reduce the reactivity of the MCP group. In addition, when substrate **1m** (R^2 = 4-$BnOC_6H_4$) was used in the reaction, the BnO group could act as a leaving group in the presence of CF_3COOH, rendering that the target product was not obtained. Furthermore, when a substrate bearing two methyl groups at the propargylic moiety was applied for this reaction with indole as the nucleophile, no reaction occurred. For the substrate having one phenyl group and one methyl group at the propargylic moiety, the corresponding by-product was mainly obtained. We attribute the results to the property of the carbocationic intermediates. The presence of aryl groups can stabilize the carbocationic intermediate formed in the propargylic moiety, and thus the process from **1** to intermediates **A**/**B** (see mechanistic explanation shown in Scheme 6) can proceed, subsequently improving the regioselectivity.

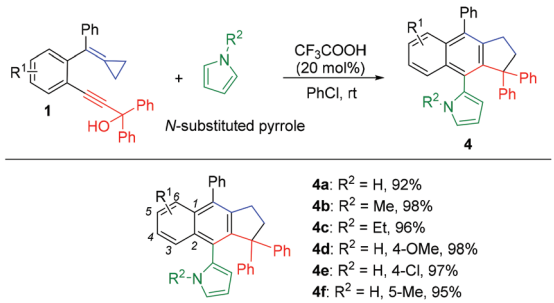
Subsequently, we also examined the substituted indoles in this reaction using **1a** as a substrate and found that similar results were obtained, affording the desired products **2o–2w** in moderate to good yields ranging from 40%–69%, suggesting that the electronic property of the substituent at the indole nucleophile did not have a significant impact on the reaction outcome (Scheme 4).



Scheme 3 Scope of the catalytic cyclization of propargylic alcohol-tethered alkylidenecyclopropanes with indole as a nucleophile. Reaction conditions: **1** (0.20 mmol, 1.0 equiv.), indole (0.20 mmol, 1.0 equiv.), CF_3COOH (0.2 equiv.), PhCl (2.0 mL) at r.t. for 6 h.



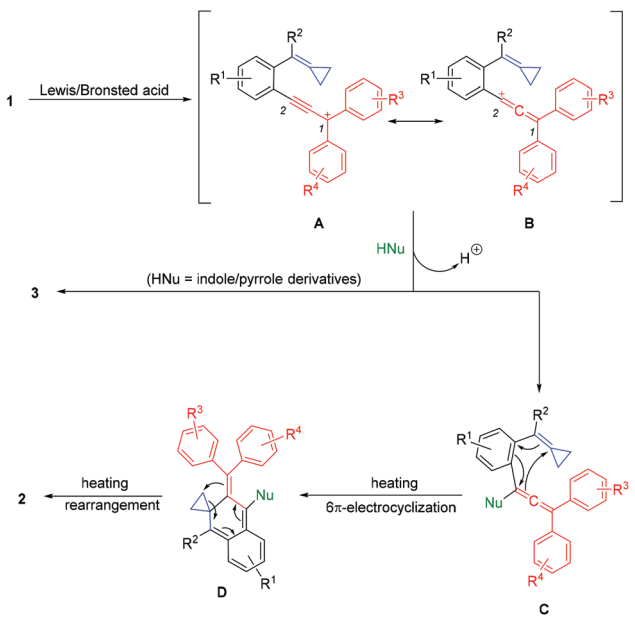
Scheme 4 Scope of the catalytic cyclization of propargylic alcohol-tethered alkylidenecyclopropanes with substituted indoles as nucleophiles. Reaction conditions: **1a** (0.20 mmol, 1.0 equiv.), substituted indole (0.20 mmol, 1.0 equiv.), CF_3COOH (20 mol%), PhCl (2.0 mL), at r.t. for 6 h. [a] Reaction conditions: **1** (0.20 mmol, 1.0 equiv.), substituted indole (0.20 mmol, 1.0 equiv.), $BF_3{\cdot}Et_2O$ (20 mol%), PhCl (2.0 mL), at r.t. for 8 h.



Scheme 5 Scope of the catalytic cyclization of propargylic alcohol-tethered alkylidenecyclopropanes with pyrrole and its derivatives as nucleophiles. Reaction conditions: **1** (0.20 mmol, 1.0 equiv.), substituted pyrrole (0.20 mmol, 1.0 equiv.), CF_3COOH (20 mol%), PhCl (2.0 mL), at r.t. for 6 h.

Using pyrrole and its derivatives as nucleophiles for this cascade nucleophilic cyclization reaction, to our delight, the corresponding products **4a–4f** were exclusively obtained in over 90% yield probably because the nucleophilicity of these pyrroles is weaker than that of indoles, leading to the nucleophilic substitution of the hydroxyl group in **1** being impossible (Scheme 5). Some other nucleophiles including furan, thiophene, imidazole, benzimidazole, and benzothiazole were used for this reaction under the standard conditions, but no corresponding product was obtained due to their weak nucleophilicity.

Based on these results and the previous reports, a plausible mechanism for this cascade nucleophilic cyclization of propargylic alcohol-tethered alkylidenecyclopropanes with pronucleophiles is proposed in Scheme 6.[6g,13] Firstly, a carbocationic intermediate was formed upon treating **1** with a Lewis/Brønsted acid. The corresponding intermediates **A** and **B** are



Scheme 6 Plausible reaction mechanism.

two types of resonances of the carbocationic intermediate. The nucleophilic attack of indole or pyrrole to the 2-position of the carbocationic intermediate afforded intermediate **C**, which underwent 6π-electrocyclization to give intermediate **D**. Then, a cyclopropane ring-opening rearrangement took place from intermediate **D** to afford the corresponding product **2**. Meanwhile, the direct nucleophilic substitution of HNu at the 1-position of the carbocationic intermediate gave by-product **3**.

Conclusions

In conclusion, we developed a novel Lewis or Brønsted acid-catalysed reaction of propargylic alcohol-tethered alkylidenecyclopropanes with indole and pyrrole derivatives for the preparation of cyclopenta[*b*]naphthalene skeletons tethered with indole and pyrrole motifs in moderate to excellent yields under mild conditions. This simple synthetic methodology avoided the use of transition metal catalysts, providing a useful tool for the synthesis of polycyclic compounds. Further exploration on the synthesis of useful polycyclic compounds with this new synthetic protocol is underway.

Experimental

General procedures for the preparation of substrates

To a stirred solution of iodine-substituted methylenecyclopropanes (1.1 equiv.) and propargylic alcohol (1.0 equiv.) in $^{i}Pr_2NH$ (30 mL), $PdCl_2(PPh_3)_2$ (2 mol%) and CuI (2 mol%) were added under an argon atmosphere. The resulting mixture was stirred at 80 °C for 8 h. After the separation of ammonium salt by filtration and the removal of solvent under reduced pressure, the residue was purified by column chromatography on silica gel to afford the corresponding substrates in good yields ranging from 85% to 98% (for more details, see chapter 3 in the ESI†).

General procedures for the synthesis of the cyclized products

To a stirred solution of propargylic alcohol-tethered alkylidenecyclopropanes (0.2 mmol) and substituted indole (0.2 mmol) in chlorobenzene (2 mL), catalyst (20 mol%) was added, and the resulting mixture was stirred at room temperature for 6 h. After removing the solvent under reduced pressure, the residue was purified by column chromatography on silica gel to afford the corresponding cyclized products.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We are grateful for the financial support from the National Basic Research Program of China [(973)-2015CB856603], the

Strategic Priority Research Program of the Chinese Academy of Sciences (Grant No. XDB20000000) and sioczz201808, the National Natural Science Foundation of China (220472096, 21372241, 21572052, 20672127, 21421091, 21372250, 21121062, 21302203, 20732008, 21772037, 21772226, 21861132014 and 91956115), and the Fundamental Research Funds for the Central Universities 222201717003.

Notes and references

1 M. A. Ernst-Russell, C. L. Chai, J. H. Wardlaw and J. A. Elix, *J. Nat. Prod.*, 2000, **63**, 129–131.
2 I. Ayumi and M. Naoyuki, JP 1560594, 2014.
3 E. Benedetti, A. B. Veliz, M. Charpenay, L. S. Kocsis and K. M. Brummond, *Org. Lett.*, 2013, **15**, 2578–2581.
4 (*a*) L. Almagro, F. Fernandez-Perez and M. A. Pedreno, *Molecules*, 2015, **20**, 2973–3000; (*b*) N. Netz and T. Opatz, *Mar. Drugs*, 2015, **13**, 4814–4914; (*c*) W. Zi, Z. Zuo and D. Ma, *Acc. Chem. Res.*, 2015, **48**, 702–711; (*d*) T. V. Sravanthi and S. L. Manju, *Eur. J. Pharm. Sci.*, 2016, **91**, 1–10; (*e*) E. Stempel and T. Gaich, *Acc. Chem. Res.*, 2016, **49**, 2390–2402; (*f*) S. Sugimoto, M. Naganuma and T. Kanai, *J. Gastroenterol.*, 2016, **51**, 853–861; (*g*) N. Chadha and O. Silakari, *Eur. J. Med. Chem.*, 2017, **134**, 159–184; (*h*) J. Bariwal, L. G. Voskressensky and E. V. Van der Eycken, *Chem. Soc. Rev.*, 2018, **47**, 3831–3848; (*i*) X. Y. Liu and Y. Qin, *Acc. Chem. Res.*, 2019, **52**, 1877–1891.
5 (*a*) R. Patil, S. A. Patil, K. D. Beaman and S. A. Patil, *Future Med. Chem.*, 2016, **8**, 1291–1316; (*b*) J. A. Homer and J. Sperry, *J. Nat. Prod.*, 2017, **80**, 2178–2187; (*c*) J. Liu, J. Cai, R. Wang and S. Yang, *Int. J. Mol. Sci.*, 2016, **18**, 20; (*d*) Y. L. Sang, W. M. Zhang, P. C. Lv and H. L. Zhu, *Curr. Top. Med. Chem.*, 2017, **17**, 120–137; (*e*) Y. Wang, F. Xie, B. Lin, M. Cheng and Y. Liu, *Chemistry*, 2018, **24**, 14302–14315; (*f*) A. Blanc and D. M. Perrin, *Pept. Sci.*, 2019, **111**, 14; (*g*) J. Kaur, D. Utreja, Ekta, N. Jain and S. Sharma, *Curr. Org. Synth.*, 2019, **16**, 17–37; (*h*) J. Lunagariya, P. Bhadja, S. Zhong, R. Vekariya and S. Xu, *Mini-Rev. Med. Chem.*, 2019, **19**, 751–761.
6 (*a*) L. Yu, M. Liu, F. Chen and Q. Xu, *Org. Biomol. Chem.*, 2015, **13**, 8379–8392; (*b*) L. Yu, J. Luan, L. Xu, Y. H. Ding and Q. Xu, *Tetrahedron Lett.*, 2015, **56**, 6116–6119; (*c*) Z. Z. Zhu, K. Chen, L. Z. Yu, X. Y. Tang and M. Shi, *Org. Lett.*, 2015, **17**, 5994–5997; (*d*) K. Chen, J. X. Liu, X. Y. Tang and M. Shi, *Chemistry*, 2016, **22**, 11549–11553; (*e*) K. Chen, X. Y. Tang and M. Shi, *Chem. Commun.*, 2016, **52**, 1967–1970; (*f*) L. Yu, F. L. Chen and Y. H. Ding, *ChemCatChem*, 2016, **8**, 1033–1037; (*g*) L. Z. Yu, X. B. Hu, Q. Xu and M. Shi, *Chem. Commun.*, 2016, **52**, 2701–2704; (*h*) L.-Z. Yu, Q. Xu, X.-Y. Tang and M. Shi, *ACS Catal.*, 2015, **6**, 526–531; (*i*) Y. Liu, Q. L. Wang, C. S. Zhou, B. Q. Xiong, P. L. Zhang, C. A. Yang and K. W. Tang, *J. Org. Chem.*, 2017, **82**, 7394–7401; (*j*) Y. Liu, Q. L. Wang, C. S. Zhou, B. Q. Xiong, P. L. Zhang, C. A. Yang and K. W. Tang, *J. Org. Chem.*, 2018, **83**, 4657–4664; (*k*) Y. Liu, Q. L. Wang, Z. Chen, Q. Zhou, H. Li, C. S. Zhou, B. Q. Xiong, P. L. Zhang and K. W. Tang, *J. Org. Chem.*, 2019, **84**, 2829–2839; (*l*) H. Cao, F. Chen, C. Su and L. Yu, *Adv. Synth. Catal.*, 2019, DOI: 10.1002/adsc.201900615.
7 (*a*) J. Ward, A. Reece, K. Li and D. Choo, *Antiviral Res.*, 2010, **86**, A69–A69; (*b*) G. Obame, P. Bremond, C. Pannecouque and G. Audran, *Synthesis*, 2013, **45**, 2612–2618; (*c*) B. J. Hunt, *Surv. Anesthesiol.*, 2014, **58**, 274–275.
8 (*a*) B. Perrin, *Revue française d'administration publique*, 2009, **132**, 711; (*b*) D. Schuster and G. Wolber, *Planta Med.*, 2010, **76**, 1179–1179.
9 (*a*) X. M. Yang, A. M. Seyam, P. F. Fu and T. J. Marks, *Macromolecules*, 1994, **27**, 4625–4626.
10 (*a*) K. W. Feng, Y. L. Ban, P. F. Yuan, W. L. Lei, Q. Liu and R. Fang, *Org. Lett.*, 2019, **21**, 3131–3135; (*b*) Y.-P. Han, X.-S. Li, M. Li, X.-Y. Zhu and Y.-M. Liang, *Adv. Synth. Catal.*, 2018, **360**, 2796–2800; (*c*) Y. P. Han, X. R. Song, Y. F. Qiu, H. R. Zhang, L. H. Li, D. P. Jin, X. Q. Sun, X. Y. Liu and Y. M. Liang, *Org. Lett.*, 2016, **18**, 940–943; (*d*) J. Y. Hu, J. Ma, Q. G. Zhu, Q. L. Qian, H. L. Han, Q. Q. Mei and B. X. Han, *Green Chem.*, 2016, **18**, 382–385; (*e*) B. Kalvacherla, S. Batthula, S. Balasubramanian and R. K. Palakodety, *Org. Lett.*, 2018, **20**, 3824–3828; (*f*) X. S. Li, Y. P. Han, X. Y. Zhu, Y. Xia, W. X. Wei, M. Li and Y. M. Liang, *Adv. Synth. Catal.*, 2018, **360**, 4441–4445; (*g*) Q. W. Song, Z. H. Zhou, M. Y. Wang, K. Zhang, P. Liu, J. Y. Xun and L. N. He, *ChemSusChem*, 2016, **9**, 2054–2058; (*h*) B. A. Trofimov, O. A. Shemyakina, A. G. Malkina, A. V. Stepanov, O. G. Volostnykh, I. A. Ushakov and A. V. Vashchenko, *Eur. J. Org. Chem.*, 2016, 5465–5469.
11 Y. Hu, H. Yao, Y. Sun, J. Wan, X. Lin and T. Zhu, *Chemistry*, 2010, **16**, 7635–7641.
12 (*a*) R. Sanz, D. Miguel, A. Martinez, M. Gohain, P. Garcia-Garcia, M. A. Fernandez-Rodriguez, E. Alvarez and F. Rodriguez, *Eur. J. Org. Chem.*, 2010, 7027–7039; (*b*) C. C. Silveira, S. R. Mendes, L. Wolf and G. M. Martins, *Tetrahedron Lett.*, 2010, **51**, 4560–4562.
13 (*a*) W. Huang, Q. Shen, J. Wang and X. Zhou, *J. Org. Chem.*, 2008, **73**, 1586–1589; (*b*) W. Huang, P. Zheng, Z. Zhang, R. Liu, Z. Chen and X. Zhou, *J. Org. Chem.*, 2008, **73**, 6845–6848; (*c*) Y. Liu, B.-D. Barry, H. Yu, J. Liu, P. Liao and X. Bi, *Org. Lett.*, 2013, **15**, 2608–2611.