



Cite this: *Chem. Commun.*, 2019, 55, 4190

Received 22nd January 2019,
Accepted 12th March 2019

DOI: 10.1039/c9cc00567f

rsc.li/chemcomm

Synthesis of polysubstituted 3-aminoindenes *via* rhodium-catalysed [3+2] cascade annulations of benzimidates with alkenes†

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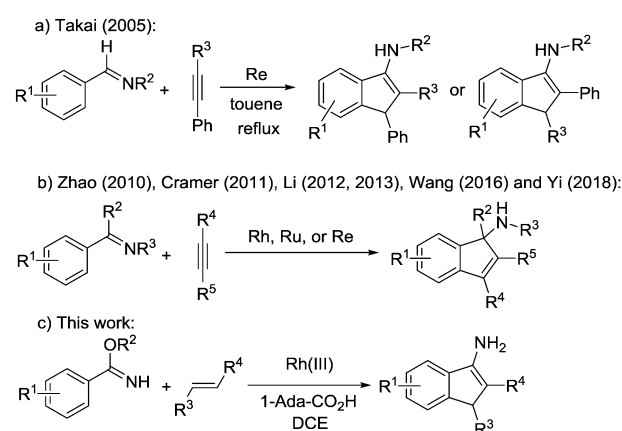
A novel Rh-catalysed intermolecular [3+2] cascade cyclization of benzimidates and alkenes has been developed to assemble polysubstituted 3-aminoindenes. The target products are important building blocks for organic synthesis and drug discovery. Cheap and easily available α,β -unsaturated ketones or nitroalkenes are applied as coupling partners. Acyl or nitro groups are easily introduced to 3-aminoindenes at the C-2 position, which makes this reaction particularly attractive for further transformation to synthesize various important building blocks.

Indenamines are key structural frameworks embedded in a large number of biologically active molecules, such as compound **A** and **B**, and exhibit a wide range of interesting pharmacological properties (Fig. 1).¹ As a result, these molecules provide an attractive platform for structure–activity relationship studies and discovery in drug development.² Therefore, novel efficient strategies to access such a skeleton are highly desirable.

Recently, direct transition-metal-catalysed intermolecular cyclization *via* C–H bond activation³ has been established as a straightforward method to construct such a core.⁴ For example, Takai and co-workers reported the first catalytic synthesis of 3-aminoindenes *via* Re catalysed cyclization of aldimines with phenyl acetylenes in 2005 (Scheme 1a).⁵ Afterwards, Zhao and co-workers reported Rh-catalysed [3+2] annulation of *N*-unsubstituted ketimines and internal alkynes to afford substituted 1-aminoindene derivatives (Scheme 1b).⁶ Subsequently, Cramer and co-workers reported an enantioselective synthesis of 1-aminoindenes *via* rhodium(i)-catalysed C–H functionalization of unsubstituted ketimines with internal alkynes (Scheme 1b).⁷ Later, Li and co-workers reported a catalytic annulation of *N*-sulfonyl imines or azomethine ylides with alkynes to form



Fig. 1 Examples illustrating the importance of indenamines.



Scheme 1 Synthesis of indenamines.

indenamines (Scheme 1b).⁸ Wang and co-workers reported a rhenium catalysed [3+2] carbocyclization of ketimines and alkynes to approach the unprotected tertiary indenamines in 2016 (Scheme 1b).⁹ More recently, Yi and co-workers reported an efficient rhodium(III)-catalysed C–H transformation of oximes for the synthesis of indenamine skeletons (Scheme 1b).¹⁰ These strategies all focused on the cycloaddition of arylimines with alkynes, which is not beneficial to expand the substrate scope. Herein, we report a protocol to polysubstitute 3-aminoindenes from benzimidates and alkenes through rhodium-catalysed C–H activation/carbocyclization (Scheme 1c). Cheap and easily

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† Electronic supplementary information (ESI) available. CCDC 1889341. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c9cc00567f

available α,β -unsaturated ketones¹¹ or nitroalkenes¹² are applied as a coupling partner. Acyl or nitro groups could be smoothly introduced to 3-aminoindenes at the C-2 position, which makes the products of this reaction particularly attractive for further transformation to synthesize various important molecules. In addition, this protocol exhibits good functional-group tolerance and excellent regioselectivity.

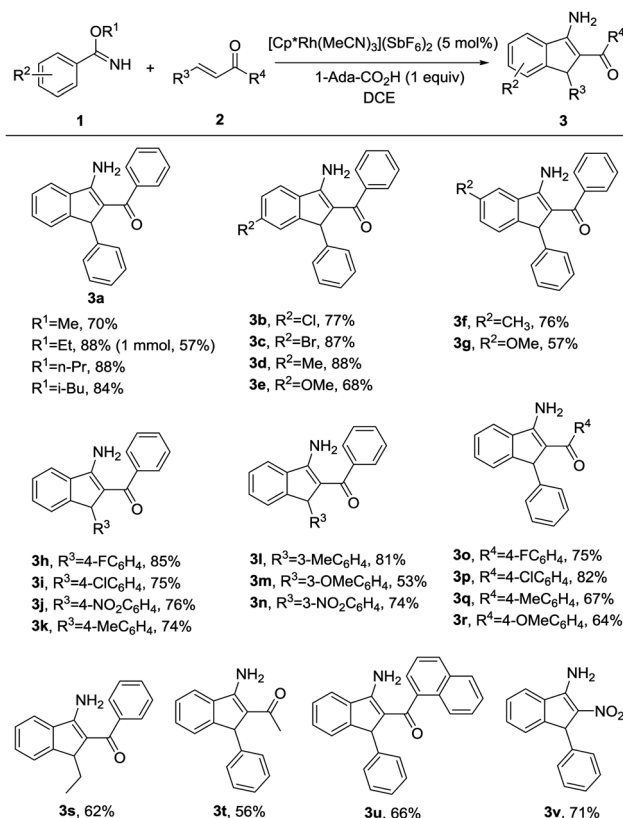
The condensation of ethyl benzimidate (**1ab**) and 1,3-diphenyl-2-propen-1-one (**2a**) was initially chosen as a model reaction to optimize the various reaction parameters (Table 1). To our great delight, the desired product **3a** was obtained in 39% yield when $[\text{Cp}^*\text{RhCl}_2]_2/\text{AgSbF}_6$ was used as a catalyst and AcOH (1 equiv.) as an additive in DCE at 120 °C under an air atmosphere (entry 1). Other metals, such as $\text{Pd}(\text{OAc})_2$, $[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$, and $[\text{Cp}^*\text{IrCl}_2]_2$ complexes, were evaluated as catalysts in our system. Unfortunately, none of them worked for this transformation (entries 2–4). A 42% yield of **3a** was obtained when $[\text{Cp}^*\text{RhCl}_2]_2/\text{AgNTf}_2$ was employed as a catalyst (entry 5). Switching the catalyst to $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$ gave a higher yield of 47% (entry 6). The reaction did not proceed smoothly without an Rh catalyst (entry 7). Then, various additives, including PivOH, 1-Ada-CO₂H, NaOAc, and LiOAc, were screened, showing that 1-Ada-CO₂H gave the highest yield (entries 8–11). The yield of **3a** was decreased to 33% in the absence of an additive (entry 12). Other solvents, such as toluene, 1,4-dioxane, and TFE, were less effective for this catalytic reaction (entries 13–15). The reaction was not significantly affected when carried out under an O₂ or N₂ atmosphere (entries 16–17).

Table 1 Optimization of the reaction conditions^a

Entry	Catalyst	Additive	Solvent	Yield ^b (%)
1	$[\text{Cp}^*\text{RhCl}_2]_2/\text{AgSbF}_6$	AcOH	DCE	39
2	$\text{Pd}(\text{OAc})_2$	AcOH	DCE	N.R.
3	$[\text{Ru}(p\text{-cymene})\text{Cl}_2]_2$	AcOH	DCE	N.R.
4	$[\text{Cp}^*\text{IrCl}_2]_2/\text{AgNTf}_2$	AcOH	DCE	N.R.
5	$[\text{Cp}^*\text{RhCl}_2]_2/\text{AgNTf}_2$	AcOH	DCE	42
6	$[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$	AcOH	DCE	47
7	—	AcOH	DCE	N.R.
8	$[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$	PivOH	DCE	48
9	$[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$	1-Ada-CO ₂ H	DCE	88
10	$[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$	NaOAc	DCE	42
11	$[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$	LiOAc	DCE	81
12	$[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$	—	DCE	33
13	$[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$	1-Ada-CO ₂ H	Toluene	51
14	$[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$	1-Ada-CO ₂ H	1,4-Dioxane	Trace
15	$[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$	1-Ada-CO ₂ H	TFE	21
16 ^c	$[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$	1-Ada-CO ₂ H	DCE	83
17 ^d	$[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$	1-Ada-CO ₂ H	DCE	89
18 ^e	$[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$	1-Ada-CO ₂ H	DCE	70
19 ^f	$[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$	1-Ada-CO ₂ H	DCE	63
20 ^g	$[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$	1-Ada-CO ₂ H	DCE	72

^a Reaction conditions: **1ab** (0.2 mmol), **2a** (2.0 equiv.), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$ (5.0 mol%), 1-Ada-CO₂H (1.0 equiv.), DCE (2 mL), 120 °C, 36 h, under an air atmosphere. ^b Isolated yields. ^c Under an N₂ atmosphere. ^d Under an O₂ atmosphere. ^e 110 °C. ^f 130 °C. ^g 24 h. N.R. = no reaction. 1-Ada-CO₂H = 1-adamantane carboxylic acid.

Table 2 Scope of the substrates^{a,b}



^a Reaction conditions: **1** (0.2 mmol), **2** (2.0 equiv.), $[\text{Cp}^*\text{Rh}(\text{MeCN})_3](\text{SbF}_6)_2$ (5.0 mol%), 1-Ada-CO₂H (1.0 equiv.), DCE (2.0 mL), 120 °C, 36 h, under an air atmosphere. ^b Isolated yields.

Changing the reaction temperature or decreasing the reaction time to 24 hours did not favor this reaction (entries 18–20).

Under the optimal reaction conditions (entry 9, Table 1), we first studied the scope and generality with respect to aryl imidates as shown in Table 2. Different alkyl groups as R¹ were used in the reaction and gave the intended product **3a** in 70–88% yields. Ethyl and *n*-propyl groups gave superior results, whereas introducing a methyl group as R¹ led to a relatively lower yield. Therefore, the ethyl group as R¹ of aryl imidates was chosen for the next study. Significantly, the transformation could be carried out on a 1 mmol scale in a reasonable yield (57%). The molecular structure of **3a** was confirmed by single-crystal X-ray diffraction analysis (Fig. 2 and ESI[†]). Aryl imidates bearing both electron-donating and electron-withdrawing groups at the *para* position of the phenyl ring all coupled smoothly with chalcone **2a** to afford the annulated products (**3b–3e**) in 68–88% yields. In the case of *meta*-substituted arylimidates, the C–H activation occurred selectively and consistently at the less hindered site, furnishing the products in good yields (**3f** and **3g**). Aryl imidates bearing a halogen atom (Cl and Br) were well tolerated under the optimized conditions to deliver the target products (**3b** and **3c**).

Subsequently, substituted α,β -unsaturated ketones were then tested using model benzyl imidate **1a** under the optimized

Fig. 2 X-ray molecular structure of **3a**.

conditions (Table 2). When R^3 and R^4 were substituted by phenyl groups, a variety of electron-donating or electron-withdrawing groups in R^3 or R^4 were well-tolerated in this transformation, producing the corresponding 3-aminoindenes in moderate to excellent yields (**3h–3r**). These results revealed that the electron density on the moiety of R^3 or R^4 did not significantly influence the efficiency of the reaction. Moreover, the corresponding 3-aminoindene could be obtained in a good yield when R^3 or R^4 was an alkyl group (**3s** and **3t**). The desired product was afforded in 66% yield when R^4 was 1-naphthyl (**3u**). It is worth mentioning that nitroalkene could also be easily converted into the corresponding product in 71% yield (**3v**), whereas terminal olefins, such as 1-hexene or styrene and olefins with ester, amide, sulfone, or other electron-withdrawing groups do not work under the standard reaction conditions.

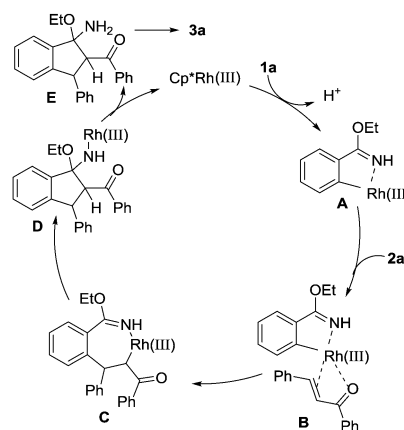
Furthermore, the resultant products obtained *via* our protocol are amenable to further chemical transformations. For example, compound **3a** could be condensed with phenylhydrazine, leading to the corresponding pyrazole in excellent yield (Scheme 2).

To further investigate the reaction mechanism, we investigated the annulation of ethyl benzimidate (**1ab**) and 1,3-diphenyl-2-propen-1-one (**2a**) under the standard reaction conditions (Scheme 3). After 3 hours, intermediate **E** was generated and detected by HRMS. However, intermediate **E** could not be detected by HRMS after 36 hours. These results suggested that the final product **3a** might be generated from intermediate **E** by the elimination of EtOH.

On the basis of the results obtained and previous reports,¹³ a plausible reaction pathway for this Rh(III)-catalysed cascade cyclization reaction is proposed and shown in Scheme 4. Firstly, coordination of the rhodium atom to the NH and the subsequent C–H activation result in the formation of the five-membered rhodacyclic intermediate **A**. Subsequently, the double bond of α,β -unsaturated ketone coordinates with the Rh atom in intermediate **A** to produce species **B**, which undergoes migratory insertion to generate seven-membered ring intermediate **C**. Then, an intramolecular nucleophilic addition leads to complex **D**. Protonation of intermediate **D** delivered the active Rh(III) species for the next catalytic cycle and intermediate **E**. Finally, elimination of EtOH as the only byproduct from **E** affords the final cyclization product **3a**.

Scheme 2 Conversion of **3a**.

Scheme 3 Control experiments.



Scheme 4 Proposed reaction mechanism.

In summary, we have successfully developed a novel and efficient synthetic route for straightforward access to 1,2-disubstituted 3-aminoindenes in moderate to excellent yields *via* rhodium(III)-catalysed intermolecular cyclization of readily available benzimidates and α,β -unsaturated ketones or nitroalkenes. This operationally simple protocol features good functional-group tolerance and excellent regioselectivity. We believe that this methodology will be widely applied in the synthesis of complex molecules bearing an aminoindene motif. Furthermore, mechanistic studies are currently underway in our laboratory.

We gratefully acknowledge the NSF of China (21572072), the Xiamen Southern Oceanographic Center (15PYY052SF01), the Science and Technology Bureau of Xiamen City (3502Z20150054), the 111 project (BC2018061) and the Subsidized Project for Cultivating Postgraduates' Innovative Ability in Scientific Research of Huaqiao University for the financial support.

Conflicts of interest

There are no conflicts to declare.

Notes and references

- For selected examples, see: (a) T. George, R. Tahiramani, C. L. Kaul and R. S. Grewal, *J. Pharm. Sci.*, 1969, **58**, 47; (b) D. T. Witiak, S. V. Kakodkar, G. E. Brunst, J. R. Baldwin and R. G. Rahwan, *J. Med. Chem.*, 1978, **21**, 1313; (c) M. Pan, T. J. Mabry, J. M. Beale and B. M. Mamiya, *Phytochemistry*, 1997, **45**, 517; (d) M. Kameyama, F. A. Siqueira, M. Garcia-Mijares, L. F. Silva and M. T. A. Silva, *Molecules*, 2011, **16**, 9421; (e) O. Svendsen, J. Arnt, V. Boeck,

- K. P. Bogeso, A. V. Christensen, J. Hyttel and J.-J. Larsen, *Drug Dev. Res.*, 1986, **7**, 35; (f) M. Suehiro, U. Scheffel, R. F. Dannals, A. A. Wilson, H. T. Ravert and H. N. Wagner, *Nucl. Med. Biol.*, 1992, **19**, 549; (g) J. Hyttel and J.-J. Larsen, *J. Neurochem.*, 1985, **44**, 1615; (h) H. Minegishi, Y. Futamura, S. Fukashiro, M. Muroi, M. Kawatani, H. Osada and H. Nakamura, *J. Med. Chem.*, 2015, **58**, 4230; (i) B. D. Dorsey, R. B. Levin, S. L. McDaniel, J. P. Vacca, J. P. Guare, P. L. Darke, J. A. Zugay, E. A. Emimi, W. A. Schleif, J. C. Quintero, J. H. Lin, I.-W. Chen, M. K. Holloway, P. M. D. Fitzgerald, M. G. Axel, D. Ostovic, P. S. Anderson and J. R. Huff, *J. Med. Chem.*, 1994, **37**, 3443; (j) D. G. Alonso, W. C. Koskinen, R. S. Oliveira, J. Constantin and S. Mislankar, *J. Agric. Food Chem.*, 2011, **59**, 13096; (k) M. Lachia, H. C. Wolf, P. J. M. Jung, C. Screpanti and A. D. Mesmaeker, *Bioorg. Med. Chem. Lett.*, 2015, **25**, 2184; (l) J. R. Courter, N. Madani, J. Sodroski, A. Schön, E. Freire, P. D. Kwong, W. A. Hendrickson, I. M. Chaiken, J. M. LaLonde and A. B. Smith III, *Acc. Chem. Res.*, 2014, **47**, 1228; (m) R. Kunstmann, U. Lerch, H. Gerhards, M. Leven and U. Schacht, *J. Med. Chem.*, 1984, **27**, 432.
- 2 For selected examples, see: (a) K. P. Bogeso, A. V. Christensen, J. Hyttel and T. Liljefors, *J. Med. Chem.*, 1985, **28**, 1817; (b) K. Andersen, T. Liljefors, K. Gundertofte, J. Perregaard and K. P. Bogeso, *J. Med. Chem.*, 1994, **37**, 950; (c) J. G. A. Walton, D. C. Jones, P. Kiuru, A. J. Durie, N. J. Westwood and A. H. Fairlamb, *ChemMedChem*, 2011, **6**, 321; (d) E. S. Burstein, J. Ma, S. Wong, Y. Gao, E. Pham, A. E. Knapp, N. R. Nash, R. Olsson, R. E. Davis, U. Hacksell, D. M. Weiner and M. R. Brann, *J. Pharmacol. Exp. Ther.*, 2005, **315**, 1278; (e) J. Parraga, S. A. Andújar, S. Rojas, L. J. Gutiérrez, N. E. Aouad, M. J. Sanz, R. D. Enriz, N. Cabedo and D. Cortes, *Eur. J. Med. Chem.*, 2016, **122**, 27; (f) J. Augstein, A. L. Ham and P. R. Leeming, *J. Med. Chem.*, 1972, **15**, 466; (g) K. P. Bogeso, J. Arnt, K. Frederiksen, H. O. Hansen, J. Hyttel and H. Pedersen, *J. Med. Chem.*, 1995, **38**, 4380; (h) M. Froimowitz, K.-M. Wu, A. Moussa, R. M. Haidar, J. Jurayj, C. George and E. L. Gardner, *J. Med. Chem.*, 2000, **43**, 4981; (i) J. Guillon, P. Dallemagne, J.-M. Léger, J. Sopkova, P. R. Bovy, C. Jarry and S. Rault, *Bioorg. Med. Chem.*, 2002, **10**, 1043; (j) K. P. Bogeso, *J. Med. Chem.*, 1983, **26**, 935.
- 3 (a) C. G. Jia, T. Kitamura and Y. Fujiwara, *Acc. Chem. Res.*, 2001, **34**, 633; (b) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731; (c) R. Giri, B.-F. Shi, K. M. Engle, N. Maugel and J.-Q. Yu, *Chem. Soc. Rev.*, 2009, **38**, 3242; (d) D.-H. Wang, K. M. Engle, B.-F. Shi and J.-Q. Yu, *Science*, 2010, **327**, 315; (e) J. Wencel-Delord, T. Drège, F. Liu and F. Glorius, *Chem. Soc. Rev.*, 2011, **40**, 4740; (f) C. Sun, B. Li and Z. Shi, *Chem. Rev.*, 2011, **111**, 1293; (g) J. Mo, L. Wang, Y. Liu and X. Cui, *Synthesis*, 2015, 439; (h) M. Wei, L. Wang, Y. Li and X. Cui, *Chin. Chem. Lett.*, 2015, **26**, 1336; (i) R. H. Crabtree and A. Lei, *Chem. Rev.*, 2017, **117**, 8481; (j) J. He, M. Wasa, K. S. L. Chan, Q. Shao and J.-Q. Yu, *Chem. Rev.*, 2017, **117**, 8754; (k) L. Wang, D. Xiong, L. Jie, C. Yu and X. Cui, *Chin. Chem. Lett.*, 2018, **29**, 907; (l) T. Yuan, C. Pi, C. You, X. Cui, S. Du, T. Wan and Y. Wu, *Chem. Commun.*, 2019, **2**, 163; (m) G. Mao, Q. Huang and C. Wang, *Eur. J. Org. Chem.*, 2017, 3549.
- 4 (a) T. Miura, T. Harumashi and M. Murakami, *Org. Lett.*, 2007, **9**, 741; (b) C.-C. Liu, R. P. Korivi and C.-H. Cheng, *Chem. – Eur. J.*, 2008, **14**, 9503; (c) H. Tsukamoto, T. Ueno and Y. Kondo, *Org. Lett.*, 2007, **9**, 3033; (d) U. Borthakur, M. Borah, M. J. Deka and A. K. Saikia, *J. Org. Chem.*, 2016, **81**, 8736; (e) S. Janody, R. Jazzar, A. Comte, P. M. Holstein, J.-P. Vors, M. J. Ford and O. Baudoin, *Chem. – Eur. J.*, 2014, **20**, 11084; (f) Z. Cao, H. Zhu, X. Meng, J. Guan, Q. Zhang, L. Tian, X. Sun, G. Chen and J. You, *Chem. – Eur. J.*, 2016, **22**, 16979; (g) J. Paul, L. L. V. My, M. Behar-Pirès, C. Guillaume, E. Léonel, M. Pisset and E. L. Gall, *J. Org. Chem.*, 2018, **83**, 4078; (h) Y. Kuninobu, H. Ueda, A. Kawata and K. Takai, *J. Org. Chem.*, 2007, **72**, 6749.
- 5 Y. Kuninobu, A. Kawata and K. Takai, *J. Am. Chem. Soc.*, 2005, **127**, 13498.
- 6 Z.-M. Sun, S.-P. Chen and P. Zhao, *Chem. – Eur. J.*, 2010, **16**, 2619.
- 7 D. N. Tran and N. Cramer, *Angew. Chem., Int. Ed.*, 2011, **50**, 11098.
- 8 (a) P. Zhao, F. Wang, K. Han and X. Li, *Org. Lett.*, 2012, **14**, 5506; (b) Y. Chen, F. Wang, W. Zhen and X. Li, *Adv. Synth. Catal.*, 2013, **355**, 353.
- 9 X. Jin, X. Yang, Y. Yang and C. Wang, *Org. Chem. Front.*, 2016, **3**, 268.
- 10 W. Gong, Z. Zhou, J. Shi, B. Wu, B. Huang and W. Yi, *Org. Lett.*, 2018, **20**, 182.
- 11 (a) F. Wang, J. Shen, G. Cheng and X. Cui, *RSC Adv.*, 2015, **5**, 73180; (b) C. Zhuang, W. Zhang, C. Sheng, W. Zhang, C. Xing and Z. Miao, *Chem. Rev.*, 2017, **117**, 7762; (c) Y. Hu, S. Li, Z. Wang, Y. Yao, T. Li, C. Yu and C. Yao, *J. Org. Chem.*, 2018, **83**, 3361; (d) H. Zhang, J. Shen, G. Cheng, B. Wu and X. Cui, *Asian J. Org. Chem.*, 2018, **7**, 1089; (e) J.-T. Yu, R. Chen, H. Jia and C. Pan, *J. Org. Chem.*, 2018, **83**, 12086.
- 12 (a) A. G. M. Barrett and G. G. Graboski, *Chem. Rev.*, 1986, **86**, 751; (b) T. J. Potter, D. N. Kamber, B. Q. Mercado and J. A. Ellman, *ACS Catal.*, 2017, **7**, 150; (c) S. Tripathi, R. Kapoor and L. D. S. Yadav, *Adv. Synth. Catal.*, 2018, **360**, 1407; (d) Y. Wang, Y. Du, X. Huang, X. Wu, Y. Zhang, S. Yang and Y. R. Chi, *Org. Lett.*, 2017, **19**, 632; (e) S. Jana, A. Chakraborty, V. Z. Shirinian and A. Hajra, *Adv. Synth. Catal.*, 2018, **360**, 2402; (f) X. Lei, L. Zheng, C. Zhang, X. Shi and Y. Chen, *J. Org. Chem.*, 2018, **83**, 1772.
- 13 (a) Y. Kuninobu, A. Kawata and K. Takai, *J. Am. Chem. Soc.*, 2005, **127**, 13498; (b) Y. Kuninobu, Y. Tokunaga, A. Kawata and K. Takai, *J. Am. Chem. Soc.*, 2006, **128**, 202; (c) S. Ye, K. Gao, H. Zhou, X. Yang and J. Wu, *Chem. Commun.*, 2009, 5406; (d) T. Fukutani, N. Umeda, K. Hirano, T. Satoh and M. Miura, *Chem. Commun.*, 2009, 5141; (e) Z.-M. Sun, S.-P. Chen and P. Zhao, *Chem. – Eur. J.*, 2010, **16**, 2619.