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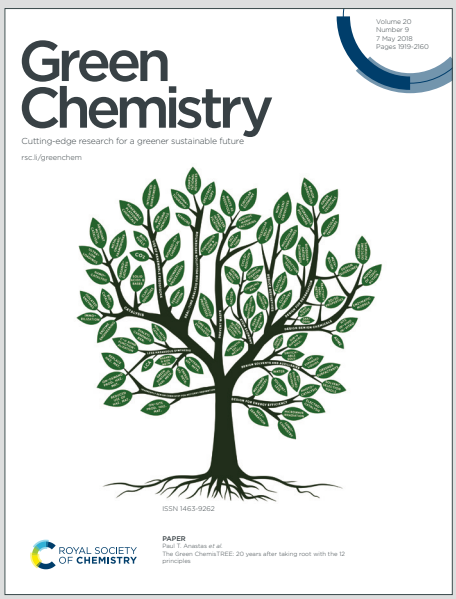

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ARTICLE

Biaryl and atropisomeric biaryl aldehyde synthesis by one-step, metal-free benzannulation of aryl enals and propiolates

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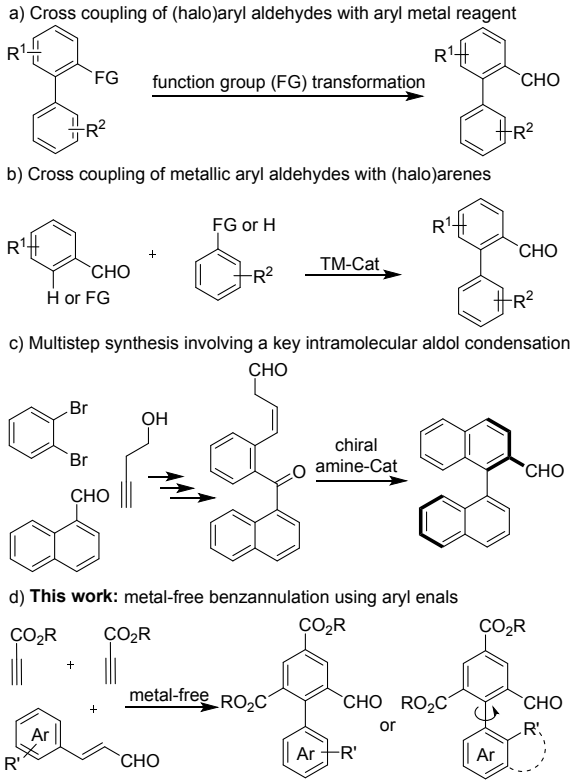
A new method involving the benzannulation of aromatic enals and two alkyl propiolate molecules has been developed as powerful route to biaryl aldehydes simply via the promotion of dimethyl amine. The benzannulation process in the absence of oxidant addtive tolerates successfully the formyl group in the enal component, leading to the straightforeward one-step synthesis of biaryl and atropisomeric aldehydes. A enamine activation based on the aza-Michael addition of dimethyl amine to the propiolate as well as the amine elimination-based generation of cyclohexadiene intermediate constitute the major factors enabling the titled reactions.

As one of the most fundamental functional groups, the formyl group in aldehydes can undergo almost of all known organic transformations. In combination with their generally long shelf stability, aldehydes are inarguably the most important, most ubiquitously employed, and irreplaceable chemicals in modern organic synthesis.[1] Particularly, as specially functionalized aldehydes, the biaryl aldehydes have in recent years been disclosed to possess much more attractive application. For example, the application as chiral fluorescent probe or chiral orgnocatalysts,[2] the convenient preparation of fused polycyclic aromatics,[3] application assisting step-economical C-H activation as transient directing group,[4] application as precursors for various axially chiral biaryl compounds,[5] to name but a few, are cutting edge domains based on the featured chemical properties of biaryl aldehydes. Therefore, the synthesis of biaryl aldehydes, especially the atropisomeric biaryl aldehydes is a highly attractive area in current science of organic synthesis.

Due to the strategic importance of biaryl aldehydes in different research and application areas, extensive efforts have been rendered to develop applicable methods for biaryl aldehyde synthesis. Beside the traditional method on functional group transformation of biaryl precursors (Scheme 1a),[6] several novel tactics have been successively reported and employed over recent years. One of the most typical accesses is the cross-coupling reactions of aryl aldehydes with a proper aromatic coupling partners via transition metal-catalyzed transformation of aryl C-H and/or other functional bonds (Scheme 1b).[7] On the other hand, Sparr and co-workers have developed a multi-step tactic for the practical synthesis of binaphthyl aldehydes on the basis of a key aldol condensation resulted annulation (Scheme 1c).[8] To sum up the known literature, it can be found that the reliance on the biaryl precursors, the use of noble metal as catalyst and/or the multi-step operation constitute the major challenges in current chemistry of biaryl aldehyde synthesis. In this regard, complementary synthetic method via the annulation of simple starting materials such as commercial aldehydes, and synthesis free of metal catalysis are highly desirable for biaryl aldehydes.

Amazingly, although simple enals have been broadly used in benzannulation reactions, the synthesis of benzaldehyde has remained as a challenge because of the rigid contradiction between the strong oxidative condition required for the



Scheme 1 Typical protocols toward biaryl aldehydes

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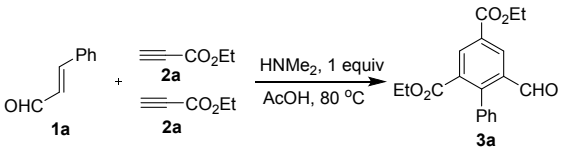
aromatisation and the sensitivity of the formyl group to oxidative conditions.[9] In 2018, our group has realized the benzannulation reaction of dienals and tertiary enaminones for the direct synthesis of benzaldehydes without consulting on any group protection or metal catalysis. The featured amine elimination generating a new double C=C bond has enabled the easy aromatisation via cyclohexadiene intermediate without effecting the formyl group, thus allowed the retainment of the formyl group in the final products.[10] Later on, other enal-based benzannulation reactions promoted by an elimination key transformation have also been developed for the synthesis of different aryl aldehydes, such as carbazole aldehydes,[11] and trifluoromethyl functionalized benzaldehydes.[12] Based on the primary success reflected by these examples, together with the individual and attractive synthetic application of stable enamines disclosed by us and others,[13-14] we envisaged that more useful synthetic methods on the benzannulation of enamines could be designed for the synthesis of valuable organic compounds such as biaryl benzaldehydes. Herein, we wish to report our results on the first benzannulation-based synthesis of biaryl aldehydes by using simple enals and alkyl propiolates as starting materials in the presence of dimethyl amine, wherein the in situ formation of enamine intermediate is utilized as a key step[15] of activation, and the amine elimination as a key step in promoting the aromatization.

To start the work, the reaction of cinnamaldehyde **1a** and two equiv ethyl propiolate **2a** were selected to probe reaction conditions. According to the typical results outlined in Table 1, employing dimethyl amine to activation the alkyne substrate was favourable (entries 1-3, Table 1). In addition, the acidic proton solvent was also required for the expected formation of **3a** (entries 4-7, Table 1). When oxidant additive such as TBHP or $K_2S_2O_8$ was added, **3a** was not observed, indicating that potent oxidant was not tolerable for the reaction (entries 8-9). Notably, increasing the loading of dimethylamine to 2 equiv could significantly enhance the yield of **3a** (entry 10, Table 1). Varying the reaction temperature, on the other hand, led to no improvement on the yield of product **3a** (entries 11-12, Table 1). When the reaction was conducted with catalytic loading of $HNMe_2$ and AcOH using EtOH as medium, much lower yield was afforded (entry 13, Table 1). Furthermore, conducting this reaction under nitrogen atmosphere gave 23% yield of **3a**, suggesting that the aerobic condition was crucial for the aromatization reaction (entry 14, Table 1).

With the proper parameters from optimization, we then investigated the application scope of this benzannulation protocol on the synthesis of biaryl aldehydes. First, the synthesis of conventional biaryl aldehydes using *para*- or *meta*-substituted cinnamaldehydes to react with alkyl propiolates. As shown in Table 2, besides unsubstituted cinnamaldehyde, different enals, including alkyl, alkoxyl, nitro and halogen substituted enals in either *para*- (**3b**-**3d**, **3g**-**3h**, **3j**-**3k**, Table 2) or *meta*-site (**3e** and **3i**, Table 2) provided corresponding products with moderate to excellent yields by reacting with different alkyl propiolates. In addition, heteroaryl-based biaryl aldehyde were also practically synthesized by using heteroaryl-based enals (**3l**-**3m**, Table 1). When two different propiolates, the ethyl and *t*-butyl propiolate were employed to react with **1a**

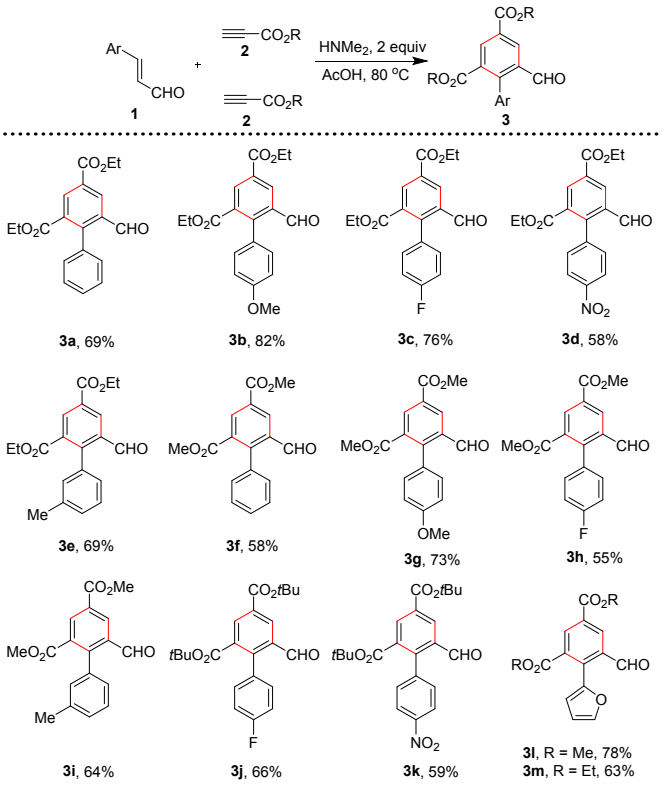
Table 1 Optimization on reaction conditions[a]



Entry	Condition variation	Yield (%)[b]
1[c]	no variation	21
2	$HNEt_2$ instead of $HNMe_2$	trace
3	piperazine instead of $HNMe_2$	15
4	DMSO instead of AcOH	trace
5	DMF instead of AcOH	trace
6	Lactic acid instead of AcOH	12
7	toluene instead of AcOH	0
8	with 1 equiv TBHP additive	0
9	with 1 equiv $K_2S_2O_8$ additive	0
10	2 equiv $HNMe_2$	69
11	2 equiv $HNMe_2$ at 70 °C	43
12	2 equiv $HNMe_2$ at 90 °C	51
13	$HNMe_2$/AcOH (0.2/0.2 equiv) in 1 mL EtOH	33
14	under nitrogen atmosphere	23

General conditions cinnamaldehyde **1a** (0.2 mmol), ethyl propiolate **2a** (0.4 mmol) in 1 mL solvent, and stirred for 12 h. [b]Yield of isolated product. [c]The 40 wt.% solution of $HNMe_2$ in water was used.

Table 2 Scope on the biaryl aldehyde synthesis[a]



[a]Yield of isolated product

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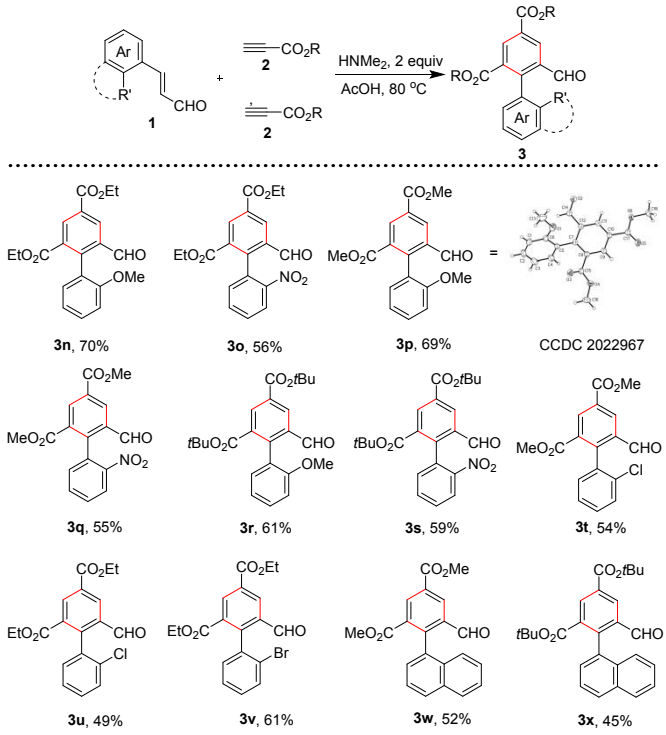
in one-pot, complex mixture was observed. Moreover, using phenylacetylene as the alternative alkyne substrate to react with **1a** was also conducted, but no biaryl aldehyde formation was observed.

As biaryl aldehydes with much higher application potential, the atropisomeric biaryl aldehydes were obviously more significant target for the synthesis. With the present benzannulation strategy, atropisomeric biaryl aldehydes could be accessed by simply employing *ortho*-substituted cinnamaldehydes or naphthyl enal as starting materials. In fact, satisfactory results on the synthesis of atropisomeric biaryl aldehydes were obtained (Table 3). The cinnamaldehydes possessing *ortho*-substituent, such as methoxyl, nitro, Cl and Br took part in the benzannulation reactions to provide the expected biaryl aldehydes with also moderate to good yields (**3n**-**3v**, Table 3). Moreover, the 2-naphthyl benzaldehydes were synthesized with fair results (**3w** and **3x**, Table 3). The atropisomeric structure of these biaryl aldehydes could be clearly observed from the single crystal structure of compound **3p**.[16]

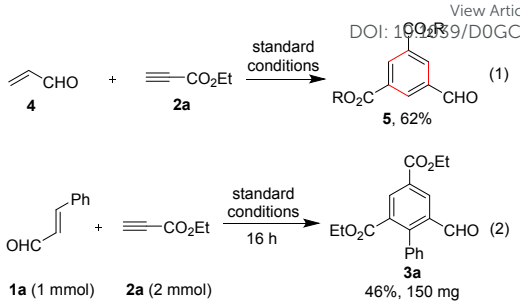
Table 3 Synthesis of atropisomeric biaryl aldehydes[a]



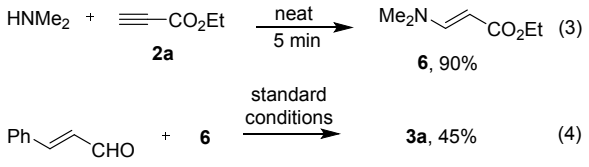
[a]Yield of isolated product

Later, as an expansion, the reaction using acrylaldehyde **4** and ethyl propiolate was also conducted, which afforded new benzaldehyde product **5** with 62% yield (Eq 1), demonstrating the broad scope of the present benzannulation method for the synthesis of diverse benzaldehyde products. In addition, a 1 mmol scale experiment on the model reaction gave product **3a** with 46% yield, suggesting that the synthetic method was potentially useful in the synthesis of biaryl aldehydes with large amount (Eq 2).

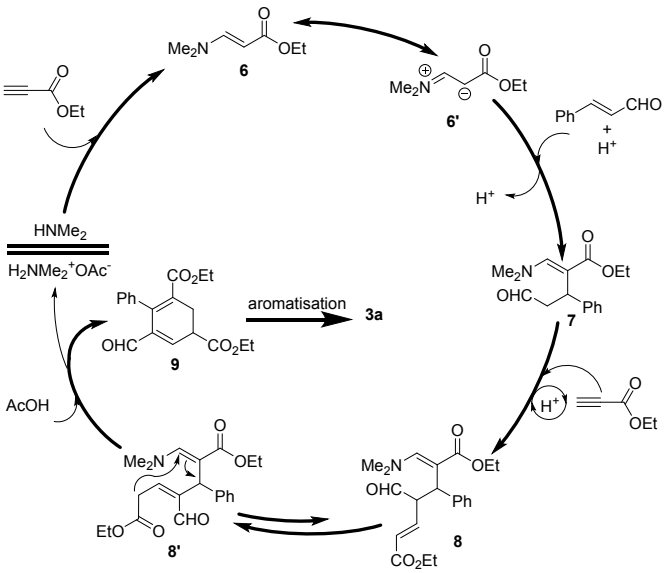
To explore the possible reaction mechanism, some control



experiments were performed. First, employing dimethyl amine with ethyl propiolate provided enaminoester **6** quickly with excellent yield under neat condition (Eq 1), indicating that **6** was a possible intermediate in the benzannulation reactions. In addition, subjecting **6** with cinnamaldehyde to the standard conditions led to the isolation of product **3a** with 45% yield (Eq 2), further supporting the enamine-based reaction pathway. On the contrary, the efforts in isolating the possible cyclohexadiene intermediate **9** (see Scheme 2) was not successful, suggesting that the aromatization from **9** to final product was a rapid transformation step.



According to the present results our previous works on the enaminone-based benzannulation and enamine activation of electron deficient alkynes,[10, 15d-e] the plausible reaction mechanism is proposed (Scheme 2). The reactions should start from the aza-Michael addition of dimethyl amine to the propiolate to generate reactive enaminoester intermediate **6**.



Scheme 2 The proposed reaction mechanism

By means the isomeric form **6'**, this intermediate incorporates to enal to provide intermediate **7** via acid-catalyzed Michael addition. Subsequently, a cascade Michael addition of the active methylene in **7** to the other propiolate molecule gives rise to intermediate **8**. In the presence of acid, the cyclization forming a new C-C bond by the nucleophilic attack of the active C-H bond in the isomeric species **8'** to provide cyclohexadiene intermediate **9** and releases dimethyl amine.[17] The easy and fast aromatisation of **9** under the aerobic atmosphere then yields the biaryl products. Since AcOH was used as the reaction medium and acid catalyst, dimethylamine may get deactivated in the acidic atmosphere by forming ammonium, explaining why stoichiometric $HNMe_2$ is required.

In conclusion, by means of enamine-based benzannulation, we have developed a rather facile and simple method for the synthesis of biaryl aldehydes and atropisomeric biaryl aldehydes. The totally metal-free conditions, stable and simple starting materials, free of formyl protection and deprotection, as well as the independence to oxidant additive constitute the unique advantage of the present method, making it a promising new option for the research and application of biaryl aldehydes.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

1 (a) J. March, Advanced Organic Chemistry: Reactions, Mechanisms, and Structure (3rd ed.), Wiley, 1985. (b) J. J. Li, Named Reactions (5th ed.), Springer, 2014. (c) L. V. R. Reddy, V. Kumar, R. Sagar and A. K. Shaw, *Chem. Rev.*, 2013, **113**, 3605.

2 (a) J. Chen, X. Gong, J. Li, Y. Li, J. Ma, C. Hou, G. Zhao, W. Yuan and B. Zhao, *Science*, 2018, **360**, 1438. (b) Y.-Y. Zhu, X.-D. Wu, S.-X. Gu and L. Pu, *J. Am. Chem. Soc.,* 2019, **141**, 175. (c) W. Wen, L. Chen, M.-J. Luo, Y. Zhang, Y.-C. Chen, Q. Ouyang and Q.-X. Guo, *J. Am. Chem. Soc.,* 2018, **140**, 9774. (d) S. Li, X.-Y. Chen and D. Enders, *Chem*, 2018, **4**, 2026. (e) Q. Wang, Q. Gu and S.-L. You, *Angew. Chem. Int. Ed.*, 2019, **58**, 2.

3 (a) H.-B. Zhao, Z.-J. Liu, J. Song and H.-C. Xu, *Angew. Chem. Int. Ed.*, 2017, **56**, 12732-12735. (b) Y. Xia, P. Qu, Z. Liu, R. Ge, Q. Xiao, Y. Zhang and J. Wang, *Angew. Chem. Int. Ed.,* 2013, **52**, 2543. (c) C. Zhu, L. Qiu, G. Xu, J. Li and J. Sun, *Chem. Eur. J.*, 2015, **21**, 12871. (d) Y. Liu, L. Chen, Z. Wang, P. Liu, Y. Liu and B. Dai, *J. Org. Chem.*, 2019, **84**, 204.

4 (a) Q.-J. Yao, S. Zhang, B.-B. Zhan and B.-F. Shi, *Angew. Chem. Int. Ed.*, 2017, **56**, 6617. (b) U. Dhawa, C. Tian, T. Wdowik, J. C. A. Oliveira, J. Hao and L. Ackermann, *Angew. Chem. Int. Ed.,* 2020, **59**, 13451. (c) Y.-J. Wu, Q.-J. Yao, H.-M. Chen, G. Liao and B.-F. Shi, *Sci. China Chem.*, 2020, **63**, 875. (d) J. Feng and Z. Gu, *Chin. J. Org. Chem.*, 2020, **40**, 1787.

5 (a) D. Guo, J. Zhang, B. Zhang and J. Wang, *Org. Lett.*, 2018, **20**, 6284. (b) C. Zhu, Y. Shi, M.-H. Xu and G.-Q. Lin, *Org. Lett.,* 2008, **10**, 1243. (c) K. Mori, T. Itakura and T. Akiyama, *Angew. Chem. Int. Ed.*, 2016, **55**, 11642.

6 (a) A. I. Meyers and K. A. Lutomski, *J. Am. Chem. Soc.,* 1982, **104**, 879. (b) M. Shindo, K. Koga and K. Tomioka, *J. Am. Chem. Soc.*, 1992, **114**, 8733. (c) M. Schlosser and F. Bailly, *J. Am. Chem. Soc.,* 2006, **128**, 16042. (d) C. Challa, J. Vellekkatt, J. Ravindran and R. S. Lankalapalli, *Org. Biomol. Chem.,* 2014, **12**, 8588.

7 (a) S. Handa, M. P. Andersson, F. Gallou, J. Reilly and B. H. Lipshutz, *Angew. Chem. Int. Ed.*, 2016, **55**, 4914. (b) H.-J. Song, W.-T. Jiang, Q.-L. Zhou, M.-Y. Xu and B. Xiao, *ACS Catal.,* 2018, **8**, 9287. (c) L. Ding, X. Sui and Z. Gu., *ACS Catal.*, 2018, **8**, 5630. (d) D. Sun, J. Du, H. Fang, J. Lan, D. Wu and J. You, *Chem. Commun.,* 2019, **55**, 7518. (e) F. Hu and M. Szostak, *Org. Lett.*, 2016, **18**, 4186.

8 (a) A. Link and C. Sparr, *Angew. Chem. Int. Ed.,* 2014, **53**, 5458. (b) R. M. Witzig, D. Lotter, V. C. Fäseke and C. Sparr, *Chem. Eur. J.,* 2017, **23**, 12960.

9 (a) D. Enders, M. R. M. Hüttl, C. Grondal and G. Raabe, *Nature,* 2006, **441**, 861. (b) T. Zhu, C. Mou, B. Li, M. Smetankova, B.-A. Song and Y. R. Chi, *J. Am. Chem. Soc.,* 2015, **137**, 5658. (c) C.-L. Zhang and S. Ye, *Org. Lett.,* 2016, **18**, 6408.

10 L. Yang and J.-P. Wan, *Chem. Commun.,* 2018, **54**, 7475.

11 D. Liu, J. Huang, F. Fu and W. Huang, *Green Chem.,* 2019, **21**, 968.

12 F. Peng, Q. Zhao, W. Huang, S.-J. Liu, Y.-J. Zhong, Q. Mao, N. Zhang, G. He and B. Han, *Green Chem.*, 2019, **21**, 6179.

13 For selected reviews, see: (a) J.-P. Wan and Y. Gao, *Chem. Rec.,* 2016, **16**, 1164. (b) A. K. Chattopadhyay and S. Hanessian, *Chem. Commun.*, 2015, **51**, 16450. (c) L. Zhang, J. Dong, X. Xu and Q. Liu, *Chem. Rev.*, 2016, **116**, 116, 287. (d) L. Fu and J.-P. Wan, *Asian J. Org. Chem.*, 2019, **8**, 767.

14 For selected recent examples, see: (a) J. Chen, P. Guo, J. Zhang, J. Rong, W. Sun, Y. Jiang and T.-P. Loh, *Angew. Chem. Int. Ed.,* 2019, **58**, 12674. (b) S. Zhou, J. Wang, L. Wang, C. Song, K. Chen and J. Zhu, *Angew. Chem. Int. Ed.,* 2016, **55**, 9384. (c) R. Xu, J.-P. Wan, H. Mao and Y. Pan, *J. Am. Chem. Soc.*, 2010, **132**, 15531. (d) X. Liang, P. Guo, W. Yang, M. Li, C. Jiang, W. Sun, T.-P. Loh and Y. Jiang, *Chem. Commun.,* 2020, **56**, 2043. (e) L. Fu, X. Cao, J.-P. Wan and Y. Liu, *Chin. J. Chem.,* 2020, **38**, 254. (f) Z. Shang, Q. Chen, L. Xing, Y. Zhang, L. Wait and Y. Du, *Adv. Synth. Catal.,* 2019, **361**, 4926. (g) Q. Yu, Y. Zhang and J.-P. Wan, *Green Chem.,* 2019, **21**, 3436. (h) X. Zheng and J.-P. Wan, *Adv. Synth. Catal.,* 2019, **361**, 5690. (i)Z.-Y. Gu, J.-J. Cao, S.-Y. Wang and S.-J. Ji, *Chem. Sci.*, 2016, **7**, 4067. (j) Y. He, J. Lou, Z. Yu and Y.-G. Zhou, *Chem. Eur. J.*, 2020, **26**, 4941. (k) K. Keskar, C. Zepeda-Velazquez, C. B. Dokuburra, H. A. Jenkins and J. McNulty, *Chem. Commun.*, 2019, **55**, 10868. (l) K. Luo, S. Mao, K. He, X. Yu, J. Pan, J. Lin, Z. Shao and Y. Jin, *ACS Catal.*, 2020, **10**, 3733.

15 For selected references on enamine activation, see: (a) S. Mukherjee, J. W. Yang, S. Hoffmann and B. List, *Chem. Rev.*, 2007, **107**, 5471. (b) K. S. Halskov, F. Kniep, V. H. Lauridsen, E. H. Iversen, B. S. Donslund and K. A. Jorgensen, *J. Am. Chem. Soc.*, 2015, **137**, 1685. (c) C. Grondal, M. Jeanty and D. Enders, *Nat. Chem.*, 2010, **2**, 167. (d) J.-P. Wan, Y. Lin, Q. Huang and Y. Liu, *J. Org. Chem.*, 2014, **79**, 7232. (e) J.-P. Wan, Y. Lin, Y. Jing, M. Xu and Y. Liu, *Tetrahedron*, 2014, **70**, 7874.

16 CCDC 2022967 contains the crystallographic data for compound **3p** reported in this paper.

17 For some known works on similar C-N cleavage for C-C bond formation, see: (a) J.-P. Wan, Y. Jing, C. Hu and S. Shou, *J. Org. Chem.*, 2016, **81**, 6826. (b) D. L. Obydennov, E. V. Chernyshova and V. Y. Sonovskikh, *J. Org. Chem.*, 2019, **84**, 6491.