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An expedient synthesis of highly functionalized 1,3-dienes by employing cyclopropenes as C_4 units†

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An efficient method has been described to synthesize dicarbonyl functionalized 1,3-dienes by cleaving the C═C bond of enaminones with cyclopropenes in the presence of a rhodium catalyst. The acetate-substituted cyclopropenes are judiciously chosen as standard C_4 units of 1,3-diene precursors. The reactions are believed to undergo a unique cutting and insertion process, involving a C═C bond cleavage of the enaminone and insertion of a new $C(sp^2)$ source with the formation of two C–C single bonds. A broad range of substrates can be used to synthesize the corresponding 1,3-dienes under very mild reaction conditions, including low catalyst-loading, ambient temperature, and a neutral reaction solvent.

1,3-Dienes are one of the most fundamental and ubiquitous organic skeletons that are widely found in pharmaceuticals, natural products, and fine chemicals (Fig. 1).[1] Significant efforts have been made to explore general and efficient synthetic methods for preparing 1,3-diene moieties.[2] Larionov *et al.* recently reported the synthesis of substituted conjugated 1,3-dienes *via* dienylation with sulfolenes as C_4 units that form sulfonates in a palladium catalytic system.[3] Inspired by these advances, we proposed to develop a general and straightforward method to construct highly functionalized 1,3-dienes by employing easily available C_4 units. For instance, from the retrosynthetic logic to the synthesis of dicarbonyl 1,3-dienes, there are three major synthetic protocols (Fig. 2): I. 1,4-Dicarbonyl compounds react with vinyl aldehydes through traditional carbonyl transformations; II. two well-polished C_4 units undergo coupling reactions; III. direct appendage of the C_4 unit of 1,3-diene with two carbonyl moieties. Although strategies I and II are efficient, they might suffer from regioselectivity problems, harsh basic conditions, and tedious steps in designing raw materials. Thus, we designed a cutting and insertion strategy III that employs substituted cyclopropenes as a new type of 1,3-diene C_4 unit precursors.

Cyclopropenes are the smallest unsaturated carbocycles and exhibit high reactivity due to ring strains.[4] In the presence of transition metal catalysts, they can open the ring *via* the C–C single bond cleavage to generate vinyl carbene complexes, which participate in numerous transformations, including X–H insertions (X = C, O, and N),[5] cyclopropanations,[6] cycloadditions,[7] and coupling reactions.[8] The obtained products typically have an additional allyl functional group. In contrast, employing cyclopropenes as 1,3-diene precursors is rarely reported.[9] We envisioned that cyclopropene with a leaving group, such as acetate, might serve as a unique 1,3-diene unit. Enaminones have attracted wide attention in recent years since their unique push–pull electronic reactivities of the C–C double bond enable various transformations in organic syntheses.[10] Furthermore, dimethylamino-substituted enaminones are easily prepared from the condensation of commercially available ketones and 1,1-dimethoxy-*N*,*N*-dimethylmethanamine. Based on continuing interest in enaminone chemistry,[11] herein, we described an expedient method to synthesize highly functionalized 1,3-dienes bearing dicarbonyl groups through the cleavage of the C═C bond of enaminones with cyclopropenes (Fig. 2, III).

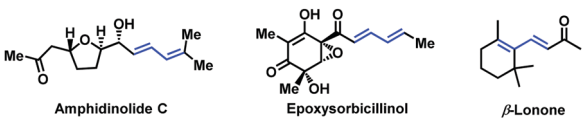

Fig. 1 Bioactive molecules carrying the 1,3-diene moiety.

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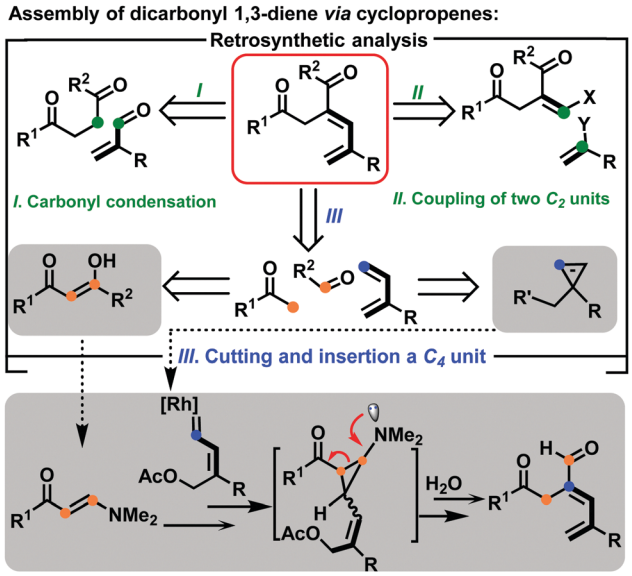
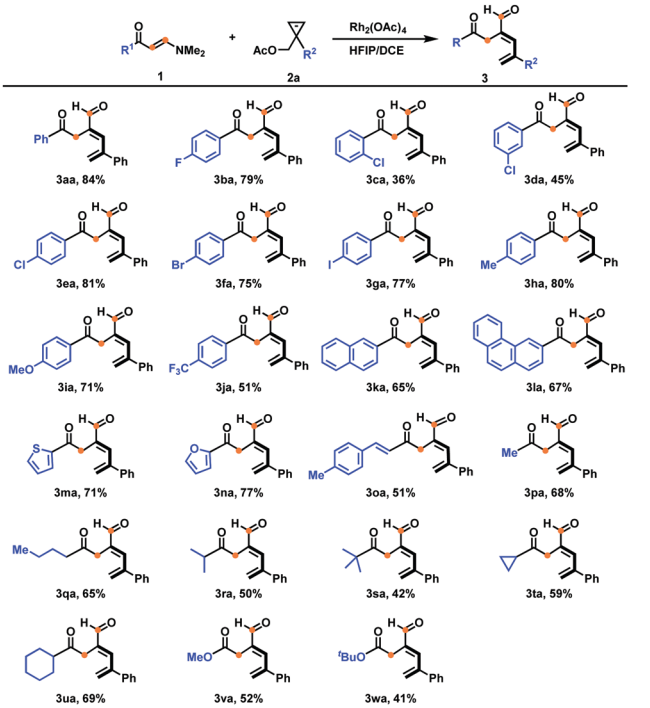


Fig. 2 Representative reaction routes to 1,3-dienes.

In the beginning, we prepared (1-phenylcycloprop-2-*en*-1-yl) methyl acetate **2a** as a model substrate to react with enaminone **1a** in the presence of different metal catalysts in dichloromethane (DCM) under nitrogen atmosphere (Table S1, see ESI,† entries 1–3). The obtained results revealed that the reaction failed to work with the copper catalyst (Table S1, entry 2), while both silver (Table S1, entry 1) and rhodium catalysts (Table S1, entry 3) successfully catalyzed the reaction to afford the conjugated 1,3-diene product **3aa** albeit in low yields. The structure and geometry of **3aa** were determined by ^{1}H NMR, ^{13}C NMR, and two-dimensional spectrum (NOESY). Then, the obvious solvent effects were observed (Table S1, entries 4–10). It showed that a more polar solvent could slightly increase the yields from 7% to 29% (Table S1, entries 4–8). The conversion of the reaction was improved significantly to 68% yield in hexafluoroisopropanol (HFIP) (Table S1, entry 9). The yield was further increased to 84% by employing 1, 2-dichloroethane (DCE) as the co-solvent (Table S1, entry 10). Then, we turned our attention to different rhodium catalysts (Table S1, entries 11–13), and found that $Rh_2(OAc)_4$ still gave the best result compared to $Rh_2(TFA)_4$, $Rh_2(Oct)_4$, and $Rh_2(esp)_2$. Finally, the optimized conditions are as follows: enaminone **1a** (0.20 mmol), cyclopropene **2a** (0.40 mmol), and $Rh_2(OAc)_4$ (1.0 mol%) were stirred in a mixed solvent system of HFIP and DCE at room temperature under nitrogen atmosphere to give 84% isolated yield (Table S1, entry 10).

Then, cyclopropenes **2** with different leaving groups were further examined under the optimized conditions to study how these leaving groups influence the reaction efficiency (Table S2, see ESI†). The results showed that cyclopropene with a free hydroxyl group **2aa** was quite stable under the rhodium catalytic system, and the starting material **1a** was recovered completely. Trifluoroacetate-substituted cyclopropene **2ab**, on the other hand, was too reactive and decomposed with unidentified complex mixtures. Pivalate **2ac**, benzoate **2ad**, and picolinate **2ae** all reacted smoothly to provide the desired 1,3-diene **3aa** in lower yields (32%–65%) compared with acetate **2a**. Methoxymethyl-substituted cyclopropene **2af** reacted with enaminone **1a** to generate vinyl aldehyde **3aa′** in 61% yield with 1 : 1 of *E*/*Z* ratio.

Table 1 Substrate scope of the enamines[ab]



[a] Conditions: **1** (0.20 mmol), **2a** (0.40 mmol), and $Rh_2(OAc)_4$ (1.0 mol%) were stirred in 2.00 mL solution (HFIP : DCE = 9 : 1) under nitrogen atmosphere. [b] Isolated yields.

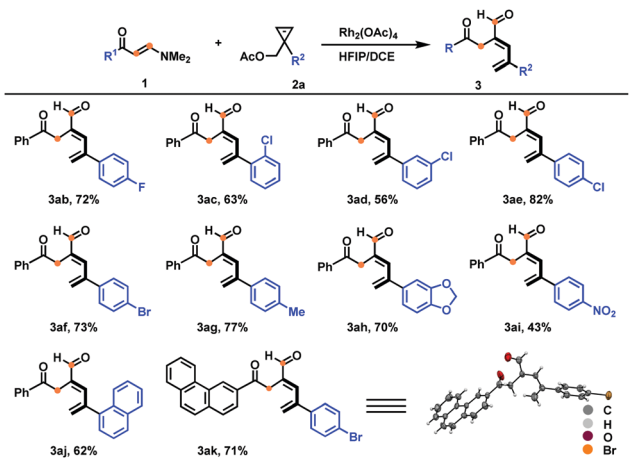
We first explored the scope of enamine substrates **1** to react with (1-phenylcycloprop-2-*en*-1-yl)methyl acetate **2a** under the optimized catalytic system (Table 1). In general, numerous substituted enaminones and enaminolates reacted smoothly to give 1,3-diene-4-aldehydes in moderate to good yields with sole *E* isomer. Aryl halide (F, Cl, Br, and I) enaminones also successfully underwent the reaction to generate the desired products in promising yields (**3ba–3ga**). The yields of *ortho*- and *meta*- aryl chlorides decreased (36% and 45%), which may be due to the steric effects (**3ca–3da**). Aryl halides (Cl, Br, and I) are general and important starting materials in transition-metal promoted name reactions such as Mizoroki–Heck reaction and Suzuki–Miyaura reaction, which allow the obtained 1,3-diene-4-aldehydes for further functionalizations.[12] Then, the electronic effects in the reactions were studied, and it was found that electron-donating substituents (**3ha–3ia**) gave higher yields (80% and 71%) than the electron-withdrawing substrate (**3ja**, 51%). Polycyclic aromatic-functionalized enaminones, such as naphthyl and phenanthryl groups, reacted smoothly to afford the dicarbonyl 1,3-dienes in moderate yields (**3ka–3la**). Heterocyclic substrates, including thienyl and furyl, also reacted well and gave the corresponding products in 71% and 77% yields,

respectively (**3ma** and **3na**). Cinnamaldehyde-derived enaminone was then examined. The result revealed that only the double bond of the enamine moiety took part in the reaction, and the conjugated C–C double bond (**3oa**) was retained. Then, the reactions of a series of alkyl-substituted enaminones were carried out under standard conditions to give the 1,3-dienes in moderate to good yields (**3pa–3ua**). The following steric effects were observed: the enaminones with primary, secondary, tertiary, and quaternary alkyl substitutions gave the desired products in a downward trend of yields from 68% to 42% (**3pa–3sa**). Furthermore, cyclic alkyl even ring-strained cyclopropyl substitutions also survived under the catalytic conditions (**3ta–3ua**). Enaminolates were then examined under the standard reaction conditions. The dicarbonyl functionalized 1,3-dienes were obtained in 52% and 41% yields, respectively (**3va–3wa**).

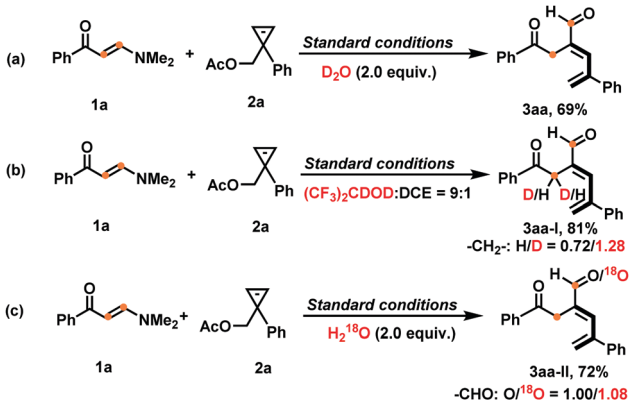
Next, the scope of the substituted cyclopropenes was examined in the same rhodium catalytic system (Table 2). On the whole, cyclopropene-bearing aryl groups reacted and constructed the desired functionalized 1,3-dienes in promising yields. Aryl halides including F, Cl, and Br could react successfully, and the corresponding products can be obtained in 56% to 82% yields (**3ab–3af**). Then, the electronic effects of the reactions were observed, and the electron-rich substituents (**3ag–3ah**) were more effective than the electron-withdrawing substituents (**3ai**). The naphthyl-substituted group also survived under the mild reaction conditions and afforded the corresponding 1,3-dienes in 62% yield (**3aj**). The structure and geometry of **3ak** were analyzed and verified using single crystal X-ray data (CCDC 2009014).

Several control experiments were then investigated to better understand the reaction mechanism (Scheme 1). Isotopic labelling experiments including D_2O and $(CF_3)_2CDOD$ were studied. The D-labelling products were found only in the methylene C–H bonds with $(CF_3)_2CDOD$ (Scheme 1a and b). It seems that

Table 2 Substrate scope of cyclopropenes[ab]



[a] Conditions: **1** (0.20 mmol), **2a** (0.40 mmol) and $Rh_2(OAc)_4$ (1.0 mol%) were stirred in 2.00 mL solution (HFIP : DCE = 9 : 1) under nitrogen atmosphere. [b] Isolated yields.

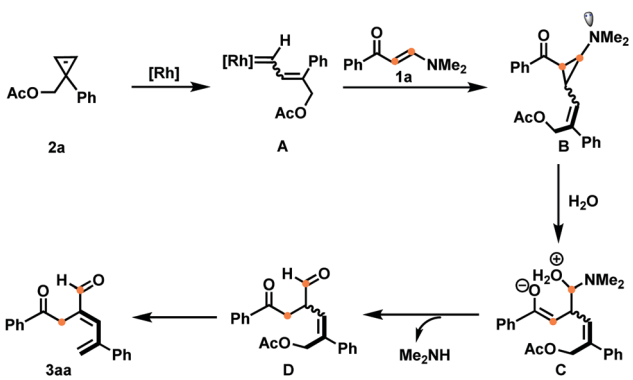


Scheme 1 Mechanism study.

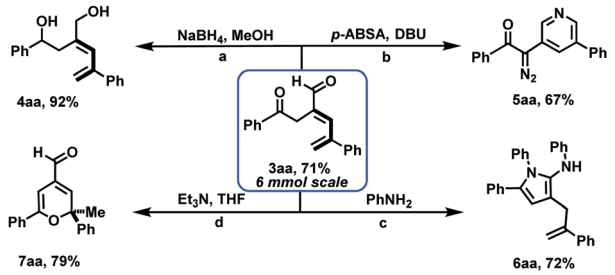
protonation/deuteration with 2.0 equivalents of D_2O might not be able to compete with the more acidic HFIP on the solvent-scale. When $H_2{}^{18}O$ was subjected to the reaction, ^{18}O was detected in the desired product **3aa-II** in 72% (Scheme 1c). These results indicate that the oxygen of the formyl group was generated from either the trace amount of water or *in situ* generated water.

Based on the obtained results, we proposed a plausible reaction pathway as described in Scheme 2. Initially, cyclopropene **2a** undergoes a ring-opening process to generate rhodium carbenoid-**A** due to the ring-strain.[13] The intermediate **A** is undergoes cyclopropanation with enaminone **1a** to afford aminocyclopropane intermediate **B**. Notably, the analogue of aminocyclopropane **B** could be isolated and reliably determined in the previous work.[11b] The push–pull electronic effect of amino and carbonyl groups may promote the regioselective C–C single bond cleavage and consequently hydrolysis to **C**.[11c] The complex **C** on further deamination affords the vinyl 1,4-ketaldehyde intermediate **D**. Finally, the intermediate **D** undergoes HOAc elimination by Me_2NH promotion to generate **3aa** as the only *E* isomer due to thermodynamic stability.[14]

The reaction was further carried out with a scale-up to 6 mmol of enaminone **1a** to demonstrate the synthetic utility of this method (Scheme 3). To our delight, the reaction worked efficiently and gave the corresponding product **3aa** in 1.17 gram (71%)



Scheme 2 Proposed mechanism.



Scheme 3 Diverse transformations.

under the catalytic $Rh_2(OAc)_4$ conditions. The obtained dicarbonyl 1,3-dienes are unique and versatile intermediates in synthetic chemistry. For instance, the dicarbonyl groups could be efficiently reduced to 1, 4-diol **4aa** in 92% isolated yield (Scheme 3a).[15] A diazo transfer reaction was then carried out with *p*-acetamidobenzenesulfonyl azide (*p*-ABSA) and DBU. Surprisingly, 3-diazo functionalized pyridine **5aa** was obtained in 67% yield (Scheme 3b). The reaction might be going through an intramolecular 6π-electrocyclization process to construct a pyridine ring (for details, see ESI†).[16] Trisubstituted pyrrole could be isolated through condensation with 2.0 equivalent aniline (Scheme 3c).[17] Notably, the 1,3-diene **3aa** could be easily transformed into substituted 2*H*-pyran with a quaternary carbon centre **7aa** (Scheme 3d).[18]

In summary, an expedient method to synthesize highly functionalized 1,3-diene derivatives from acetate substituted cyclopropenes and enaminones has been described. The reaction is believed to undergo a cascade process involving carbene insertion, amino-directed ring-opening, and acetic acid elimination reactions. It is demonstrated for the first time that acetate substituted cyclopropenes can be employed as a unique C_4 unit of 1,3-diene precursors. This novel strategy is accomplished under very mild reaction conditions, including low catalyst-loading and ambient reaction temperature, which further enable step-economy and environmental benefit.

Conflicts of interest

The authors declare no competing financial interest.

Notes and references

1 (*a*) G. Mehta and H. S. P. Rao, *The Chemistry of Dienes and Polyenes; Z. Rappoport*, Wiley, New York, 1997; (*b*) V. H. Rawal and S. A. Kozmin, *1,3-Dienes. Science of Synthesis*, Georg Thieme Verlag KG, Stuttgart, 2009; (*c*) J. H. Delcamp, P. E. Gormisky and M. C. White, *J. Am. Chem. Soc.*, 2013, **135**, 8460–8463; (*d*) A. M. Harned and K. A. Volp, *Nat. Prod. Rep.*, 2011, **28**, 1790–1810; (*e*) H. Zorn, S. Langhoff, M. Scheibner, M. Nimtz and R. G. Berger, *Biol. Chem.*, 2003, **384**, 1049–1056.
2 (*a*) S. T. Diver and A. J. Giessert, *Chem. Rev.*, 2004, **104**, 1317–1382; (*b*) M. D. Paolis, I. Chataigner and J. Maddaluno, *Top. Curr. Chem.*, 2012, **327**, 87–146; (*c*) X. Shang and Z.-Q. Liu, *Chem. Soc. Rev.*, 2013, **42**, 3253–3260; (*d*) C. Liu, J. Yuan, M. Gao, S. Tang, W. Li, R. Shi and A. Lei, *Chem. Rev.*, 2015, **115**, 12138–12204.
3 (*a*) V. T. Nguyen, H. T. Dang, H. H. Pham, V. D. Nguyen, C. Flores-Hansen, H. D. Arman and O. V. Larionov, *J. Am. Chem. Soc.*, 2018, **140**, 8434–8438; (*b*) H. T. Dang, V. D. Nguyen, G. C. Haug, N. T. C. Vuong, H. D. Arman and O. V. Larionov, *ACS Catal.*, 2021, **11**, 1042–1052.
4 (*a*) V. Rubén, *Chem. Rev.*, 2021, **121**, 162–226; (*b*) Y. Wang, E. A. F. Fordyce, F. Chen and H. Lam, *Angew. Chem., Int. Ed.*, 2008, **47**, 7350–7353; (*c*) S. Ma, J. Zhang, Y. Cai and L. Lu, *J. Am. Chem. Soc.*, 2003, **125**, 13954–13955; (*d*) H. Zhang, K. Wang, B. Wang, H. Yi, F. Hu, C. Li and J. Wang, *Angew. Chem., Int. Ed.*, 2014, **53**, 13234–13238; (*e*) B. R. Elling and Y. Xia, *J. Am. Chem. Soc.*, 2015, **137**, 9922–9926.
5 (*a*) M. Rubin, M. Rubina and V. Gevorgyan, *Chem. Rev.*, 2007, **107**, 3117–3179; (*b*) I. Marek, S. Simaan and A. Masarwa, *Angew. Chem., Int. Ed.*, 2007, **46**, 7364–7376; (*c*) S. Mata, L. A. López and R. Vicente, *Angew. Chem., Int. Ed.*, 2018, **57**, 11422–11426; (*d*) S. Mata, L. A. López and R. Vicente, *Angew. Chem., Int. Ed.*, 2017, **56**, 7930–7934; (*e*) Y. Deng, C. Jing, P. Y. Zavalij and M. P. Doyle, *Org. Lett.*, 2015, **17**, 4312–4315; (*f*) J. T. Bauer, M. S. Hadfield and A.-L. Lee, *Chem. Commun.*, 2008, 6405–6407.
6 (*a*) F. Miege, C. Meyer and J. Cossy, *Org. Lett.*, 2010, **12**, 4144–4147; (*b*) F. Miege, C. Meyer and J. Cossy, *Angew. Chem., Int. Ed.*, 2011, **50**, 5932–5937; (*c*) F. Miege, C. Meyer and J. Cossy, *Chem. – Eur. J.*, 2012, **18**, 7810–7822; (*d*) M. J. González, J. González, L. A. López and R. Vicente, *Angew. Chem., Int. Ed.*, 2015, **54**, 12139–12143.
7 (*a*) M. F. Semmelhack, S. Ho, M. Steigerwald and M. C. Lee, *J. Am. Chem. Soc.*, 1987, **109**, 4397–4399; (*b*) C. Li, Y. Zeng, H. Zhang, J. Feng, Y. Zhang and J. Wang, *Angew. Chem., Int. Ed.*, 2010, **49**, 6413–6417; (*c*) X.-B. Wang, Z.-J. Zheng, J.-L. Xie, X.-W. Gu, Q.-C. Wu, G.-W. Yin, F. Ye, Z. Xu and L.-W. Xu, *Angew. Chem., Int. Ed.*, 2020, **59**, 790–797; (*d*) H. Zheng and M. P. Doyle, *Angew. Chem., Int. Ed.*, 2019, **58**, 12502–12506.
8 (*a*) J. M. Fox and N. Yan, *Curr. Org. Chem.*, 2005, **9**, 719–732; (*b*) A. Masarwa, A. Stanger and I. Marek, *Angew. Chem., Int. Ed.*, 2007, **46**, 8039–8042; (*c*) Y. Zhou, B. G. Trewyn, R. J. Angelici and L. K. Woo, *J. Am. Chem. Soc.*, 2009, **131**, 11734–11743; (*d*) R. Vicente, J. González, L. Riesgo, J. González and L. A. López, *Angew. Chem., Int. Ed.*, 2012, **51**, 8063–8067; (*e*) H. Zhang, B. Wang, K. Wang, G. Xie, C. Li, Y. Zhang and J. Wang, *Chem. Commun.*, 2014, **50**, 8050–8052; (*f*) B. Wang, H. Yi, H. Zhang, T. Sun, Y. Zhang and J. Wang, *J. Org. Chem.*, 2018, **83**, 1026–1032.
9 (*a*) M. G. Steinmetz, Y.-P. Yen and G. K. Poch, *J. Chem. Soc., Chem. Commun.*, 1983, **24**, 1504–1505; (*b*) J.-Q. Huang and C.-Y. Ho, *Angew. Chem., Int. Ed.*, 2019, **58**, 5702–5706.
10 (*a*) J.-P. Wan and Y. Gao, *Chem. Rec.*, 2016, **16**, 1164–1177; (*b*) J. Huang and F. Yu, *Synthesis*, 2021, 587–610.
11 Representative works of enaminones: (*a*) F. Wang, W. Sun, Y. Wang, Y. Jiang and T.-P. Loh, *Org. Lett.*, 2018, **20**, 1256–1260; (*b*) J. Chen, P. Guo, J. Zhang, J. Rong, W. Sun, Y. Jiang and T.-P. Loh, *Angew. Chem., Int. Ed.*, 2019, **58**, 12674–12679; (*c*) G. Liang, J. Rong, W. Sun, G. Chen, Y. Jiang and T.-P. Loh, *Org. Lett.*, 2018, **20**, 7326–7331; (*d*) M. Ni, J. Zhang, X. Liang, Y. Jiang and T.-P. Loh, *Chem. Commun.*, 2017, **53**, 12286–12289; (*e*) Y. Jiang, G. Liang, C. Zhang and T.-P. Loh, Eur, *J. Org. Chem.*, 2016, **20**, 3326–3330; (*f*) X. Liang, P. Guo, W. Yang, M. Li, C. Jiang, W. Sun, T.-P. Loh and Y. Jiang, *Chem. Commun.*, 2020, **56**, 2043–2046; (*g*) S. Zhou, J. Wang, L. Wang, C. Song, K. Chen and J. Zhu, *Angew. Chem., Int. Ed.*, 2016, **55**, 9384–9388; (*h*) E. Lourdusamy, L. Yao and C.-M. Park, *Angew. Chem., Int. Ed.*, 2010, **49**, 7963–7967; (*i*) L. Gan, Q. Yu, Y. Liu and J.-P. Wan, *J. Org. Chem.*, 2021, **86**, 1231–1237; (*j*) K. K. Toh, A. Biswas, Y.-F. Wang, Y. Y. Tan and S. Chiba, *J. Am. Chem. Soc.*, 2014, **136**, 6011–6020.
12 (*a*) D. Liu, H.-X. Ma, P. Fang and T.-S. Mei, *Angew. Chem., Int. Ed.*, 2019, **58**, 5033–5037; (*b*) F. Bellina and R. Rossi, *Chem. Rev.*, 2010, **110**, 1082–1146.
13 (*a*) A. Archambeau, F. Miege, C. Meyer and J. Cossy, *Angew. Chem., Int. Ed.*, 2012, **51**, 11540–11544; (*b*) H. Zhang, B. Wang, H. Yi, Y. Zhang and J. Wang, *Org. Lett.*, 2015, **17**, 3322–3325; (*c*) Y. Lou, T. P. Remarchuk and E. J. Corey, *J. Am. Chem. Soc.*, 2005, **127**, 14223–14230.
14 (*a*) C. Li, Y. Zeng and J. Wang, *Tetrahedron*, 2009, **50**, 2956–2959; (*b*) M. Simaan, P.-O. Delaye, M. Shi and I. Marek, *Angew. Chem., Int. Ed.*, 2015, **54**, 12345–12348.
15 H. Suzuki, S. Yoshioka, A. Igesaka, H. Nishioka and Y. Takeuchi, *Tetrahedron*, 2013, **69**, 6399–6403.
16 (*a*) Y. Jiang and C.-M. Park, *Chem. Sci.*, 2014, **5**, 2347–2351; (*b*) Y. Jiang, C.-M. Park and T.-P. Loh, *Org. Lett.*, 2014, **16**, 3432–3435.
17 C. Zhu, R. Zhu, H. Zeng, F. Chen, C. Liu, W. Wu and H. Jiang, *Angew. Chem., Int. Ed.*, 2017, **56**, 13324–13328.
18 T.-L. Shie, C.-H. Lin, S.-L. Lin and D.-Y. Yang, *Eur. J. Org. Chem.*, 2007, 4831–4836.