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Letter

Pd-Catalyzed Triple-Fold C(sp^2)−H Activation with Enaminones and Alkenes for Pyrrole Synthesis via Hydrogen Evolution

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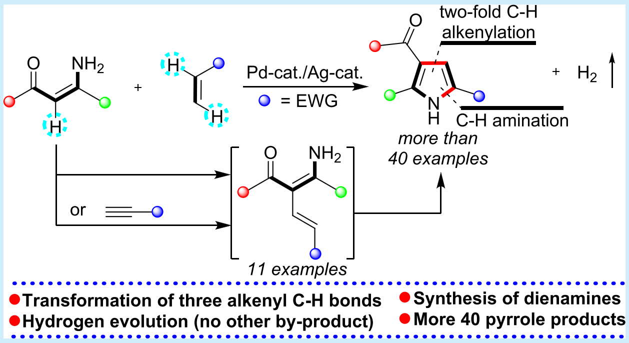
ABSTRACT: The synthesis of NH-free pyrroles via Pd-catalyzed annulation of enaminones and alkenes is reported. With the catalysis of Pd(II), the activation of triple C(sp^2)−H bonds, including one internal C(sp^2)−H bond in enaminone, has been activated to provide various pyrroles. The interesting evolution of hydrogen gas from the reactions has been observed by a hydrogen detector.



As one of the fundamental heteroaryl motifs showing prevalent applications in multidisciplinary areas,[1] the pyrrole ring has been an attractive target throughout the development of synthetic chemistry. The classical Paal−Knorr reaction,[2] Knorr reaction,[3] and Hantzsch reaction,[4] for example, have contributed enormously to the advances of pyrrole chemistry. However, following the daily increasing demand in molecular diversity-, sustainability-, and safety-oriented synthetic strategies, devising alterative and/or complementary methods for pyrrole synthesis has emerged as a significant goal in the science of synthesis.[5] As one novel example of a newly emerged tool in pyrrole synthesis, the cascade annulation involving the key activation of one or more C−H bonds has brought an important breakthrough. For example, Stuart and co-workers reported the Rh(III)/Cu(II)-catalyzed annulation of enamides and alkynes for pyrrole synthesis via a key addition of the enamide C−H bond to the alkyne.[6] Glorius et al. developed the pyrrole ring construction via Pd(II)-catalyzed intramolecular C−H alkenylation of imines.[7] Ellmann and co-workers disclosed the reactions of enone-derived oxime esters and imines for pyrrole synthesis via Rh-catalyzed alkenyl C−H functionalization.[8] In addition, reactions featured with C−H bond conversion in various other substrates have also been developed as practical protocols toward diverse pyrrole scaffolds.[9]

Among the designated methods for pyrrole synthesis via C−H activation or functionalization, however, enamines have been identified as most frequently used and reliable substrates. With the catalysis of proper transition metal reagents, stable enamines such as enaminones, enaminoesters, enaminonitriles, etc. have been used to couple alkynes,[10] alkenes,[11] diazoesters/hydrazones,[12] or functionalization of intramolecular C−H bonds[13] for the synthesis of diversely functionalized pyrroles. Interestingly, although a plethora of different alkenes have been successfully used as reaction partners of stable enamines for pyrrole synthesis, no known method has hitherto been found to tolerate the transformation of acrylates for the synthesis of corresponding pyrrole products. Considering the important and broad application of acrylates in the C−H alkenylation reactions,[14] it is thus highly demanding to establish new methods by activating the C−H bond of acrylates and enamines for the synthesis pyrroles with expanded product diversity.

Recently, the dehydrogenative transformations on C−H and/or heteroatom-H bonds via hydrogen evolution has emerged as a drastically sustainable tool in constructing new C−C or C−heteroatom bonds.[15] Actually, the dehydrogenation of alcohols and amino alcohols has already been realized with significant success in the synthesis of pyrroles by releasing the hydrogen gas via alcohol transformation.[16] However, hydrogen evolution via the activation of the stable C−H bond has not yet been reported for the construction of a pyrrole ring. In combination with the recent progress in the vinyl C−H activation and functionalization disclosed by us and others[17] as well as the recent emphasis in developing novel synthetic methods via aryl ring construction using polar alkenes,[18] we report herein a new method on the synthesis of pyrroles via

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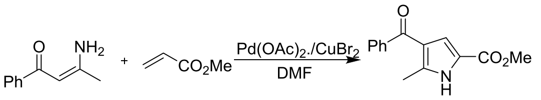
hydrogen evolution-based coupling of three stable C−H bonds and an N−H bond by the reactions of simple enaminones and acrylates. In addition, the synthesis of conjugate dienamines has also been realized via catalytic addition of enaminones to propiolates. The efficient transformation of these dienamines into the titled pyrroles has provided strong evidence in elucidating the possible reaction mechanism.

Initially, the reaction of enaminone **1a** and methyl acrylate **2a** was conducted under different conditions for the synthesis of pyrrole product **3a**. Systematical screening on the catalyst, additive, medium, temperature, reagents loading, etc. was executed (see full data in the Supporting Information). As outlined by the typical data (Table 1), the simultaneous employment of Pd(II) and Cu(II) reagent was mandatory (entries 1−4, Table 1). In addition, conducting the reaction at a mild temperature of 60 °C was favorable to give better results (entries 5−6, Table 1). On the other hand, increasing the loading of **2a** also proved to be practical in improving the product yield (entry 7, Table 1). Notably, reducing the volume of reaction medium and employing additionally AgOAc as additive was able to further enhance the yield of **3a**, respectively (entries 7−9, Table 1).

Table 1. Typical Results on the Condition Optimization[a]



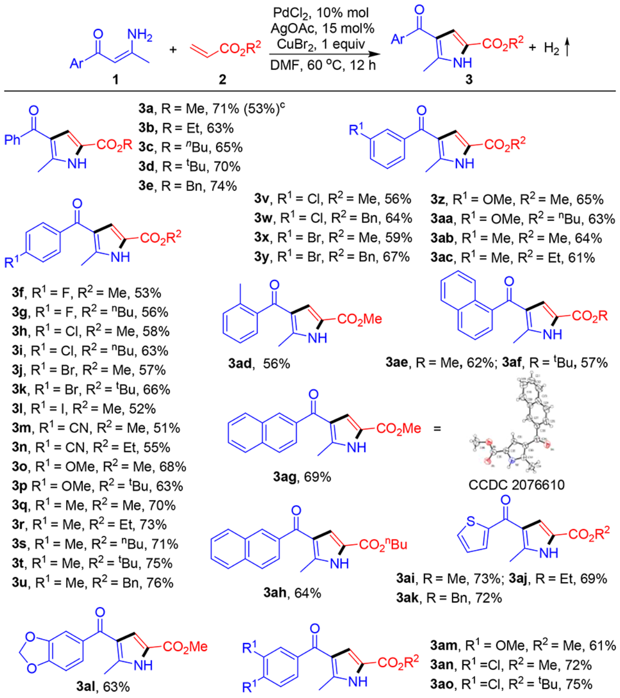
1a **2a** **3a**

entry	variation from the general conditions	yield (%)[b]
1	no variation	43
2	$Pd(OAc)_2$ (0.01 mmol) and $CuBr_2$ (0.1 mmol)	24
3	$Pd(OAc)_2$ (0.01 mmol), no $CuBr_2$	0
4	$CuBr_2$ (0.1 mmol) and no $Pd(OAc)_2$	0
5	reaction at 40 °C	44
6	reaction at 60 °C	48
7	with 0.7 mmol **2a**, at 60 °C	55
8[c]	with 0.7 mmol **2a**, 60 °C	63
9[c]	with 0.7 mmol **2a**, 60 °C and 0.5 mL of DMF	71

[a] General conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), $CuBr_2$ (0.2 mmol) in DMF (2 mL). Stirred at 80 °C for 12 h. [b] Isolated yield. [c] With additional AgOAc (0.03 mmol).

Under the optimal conditions, the scope and limitations of this method in synthesizing pyrroles **3** were investigated.[19] On one hand, when enaminone **1a** was fixed to react with different acrylic ester substrates, the products containing a methyl, ethyl, *n*-butyl, *tert*-butyl, or benzyl group (**3a**−**3e** and **3q**−**3u**, Scheme 1) were afforded in good yields. The extension of the alkene component to internal alkenyl ester, enone, vinyl nitrile, vinyl amide, styrene, and α-allylnaphthalene was also conducted, but none gave the expected pyrrole product under the present conditions (see also Scheme S2 in the Supporting Information). For the enaminones **1**, on the other hand, electron-withdrawing groups such as F, Cl, Br, I, and CN (**3f**−**3n** and **3v**−**3y**, Scheme 1) and electron-donating groups such as alkyl- and alkoxyl-substituted phenyl enaminones (**3o**−**3u**, **3z**−**3ac**, Scheme 1) showed general tolerance to the synthesis. Slightly lower yields were observed in the reactions employing enaminones functionalized with electron-withdrawing groups. Moreover, enaminones featuring more than one substituent in the phenyl ring also took part in the synthesis to afford good results (**3al**−**3ao**, Scheme 1). As expected, the synthesis of pyrroles bearing fused aryl (**3ag** and **3ah**, Scheme 1) and heteroaryl groups (**3ag** and **3ah**, Scheme 1) were also smoothly acquired by employing corresponding fused and heteroaryl-functionalized enaminones. Nevertheless, no expected products were observed when N-substituted enaminones, dimedone-derived cyclic NH_2-enaminone, and pentane-2,4-dione-derived alkyl NH_2-enaminone was independently used to react with acrylate **2a** under the standard conditions (Scheme S2 in the Supporting Information). Additionally, the reaction of aniline with **2a** was conducted with the standard catalytic conditions. However, no evident reaction was observed.

Scheme 1. Substrate Scope on Pyrrole Synthesis[a,b]

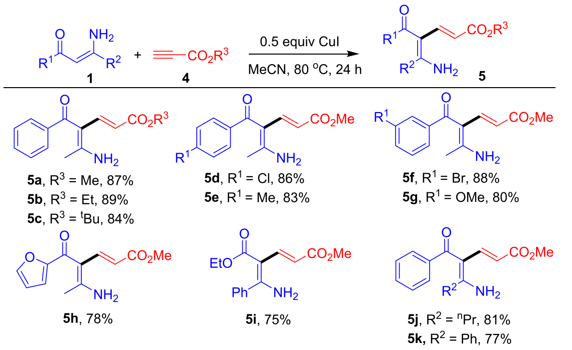


[a] Reaction conditions: **1** (0.2 mmol), **2** (0.7 mmol), DMF (0.5 mL), reacted under air for 12 h. [b] The H_2 was detected by H_2 detector. [c] Yield from 1 mmol scale reaction.

Interestingly, by means of modifying the reaction conditions, we were pleased to find that CuI could catalyze the C−H bond addition of enaminones to alkyl propiolates **4** for the selective synthesis of conjugate dienamines **5** with good to excellent yields. As depicted in Scheme 2, different alkyl acrylates (**5a**−**5c**, Scheme 2), as well as enaminones possessing functional groups such as halogen, methyl, methoxy, etc. in either the *meta* or *para* position (**5d**−**5g**, Scheme 2) provided corresponding products with satisfactory yields. Notably, this C−H addition also tolerated well the furan-functionalized enaminone and enaminoester (**5h** and **5i**, Scheme 2). Corresponding dienamines with different β-substitutions (R^2 = *n*-Pr or Ph) were also practically furnished (**5j** or **5k**, Scheme 2).

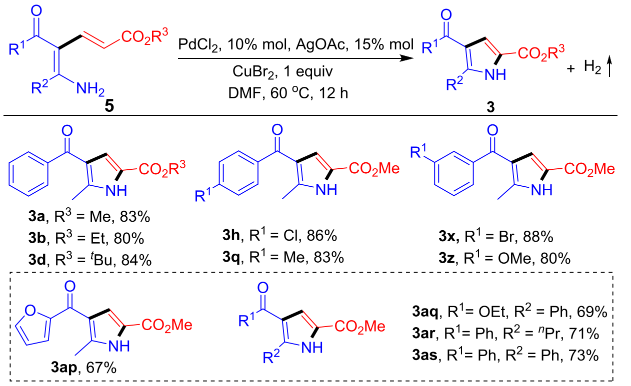
Having been inspired by the tunable synthesis of dienamines **5**, we thought that such compounds were the possible intermediate during the formation of the pyrrole products. Accordingly, these dienamines were found to undergo intramolecular dehydrogenative C−H amination to provide pyrroles **3** with high efficiency under the standard Pd-catalytic conditions. Besides providing products that had been

Scheme 2. Synthesis of Conjugate Dienamines[a]



[a]Reaction conditions: **1** (0.2 mmol), **4** (0.4 mmol), MeCN (2.0 mL), stirred under air for 24 h; isolated yield was reported.

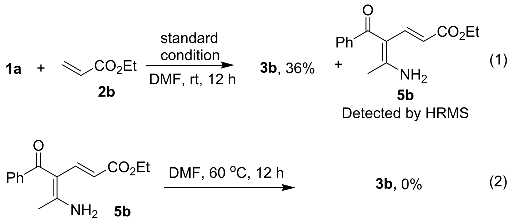
Scheme 3. Synthesis of Pyrroles from Various Dienamines[a,b]



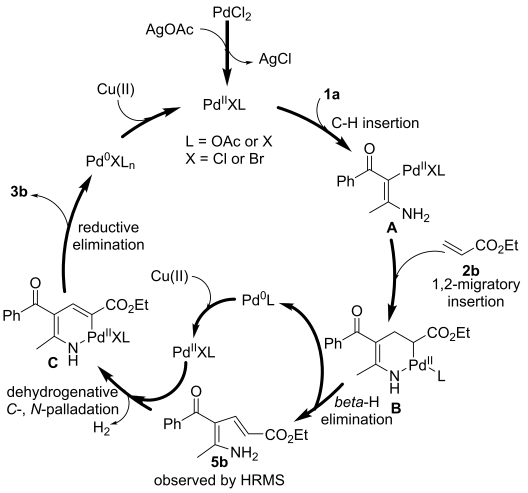
[a]Reaction conditions: **5** (0.2 mmol) in DMF (0.5 mL), stirred for 12 h under air; isolated yield was reported. [b]The H_2 was detected by H_2 detector.

synthesized via the direct enamine−acrylate annulation (**3a**,**b**, **3d**, **3h**, **3q**, **3x**, and **3z**, Scheme 3), the intramolecular version was found to be capable of providing new pyrrole products that could not be accessed by the above annulation protocol (**3ap**−**3as**, Scheme 3). Moreover, hydrogen evolution was observed from the reaction, further supporting that **5** were key reaction intermediates also in the enamine−acrylate annulation. However, directly employing enaminone **1a** and methyl propiolate (**4a**) to the standard conditions in Scheme 1 did not provide pyrrole **3a**.

For the sake of gaining more information on the reaction process, some control experiments were also designed. First, pyrrole **3b** and dienamine **5b** were obtained by performing the reaction of **1a** and **2a** at room temperature (eq 1). In addition, **3b** could not be obtained without employing the metal reagents, confirming the indispensable role of metal in the reaction (eq 2).



Scheme 4. Plausible Reaction Mechanism



According to the clues provided by the control experiments, a mechanism for this NH-free pyrrole synthesis has been proposed. As outlined in Scheme 4, the reaction of AgOAc and $PdCl_2$ may provide active $Pd^{II}XL$ which couples enaminone to deliver Pd(II) intermediate **A** via the C−H insertion.[20] The 1,2-migratory insertion of the alkene to A leads to the formation of palladacycle species B. The featured β-H elimination from **B** provides dienamine intermediate **5b**, which has been observed with HMRS from the reaction residue (see the Supporting Information). The dehydrogenative C-,N-palladation of **5b** with Pd(II) gives rise to palladacycle **C**, which undergoes reductive elimination to yield the pyrrole product. The Pd(0) released thereby can be regenerated in the presence of a Cu(II) terminal oxidant.

In conclusion, we have developed a method for the synthesis of NH-free pyrroles with the dehydrogenative coupling of enaminones and alkenes via Pd-catalyzed activation of triple $C(sp^2)$−H bonds. The reaction represents a good tolerance of a broad scope of enaminones and acrylates. In addition, we also obtained a variety of conjugate dienamines by utilizing various enaminones and propiolates, and the dienamines could be transformed to NH-free pyrroles under optimal conditions. Mechanistic studies suggested that dienamine was most likely to be an active intermediate during the whole reaction.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c01301.

> Experimental procedures, hydrogen gas determination, characterization data, and HRMS and NMR spectra (PDF)

Accession Codes

CCDC 2076610 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Shimizu, S. Recent Advances in Subporphyrins and Triphyrin Analogues:Contracted Porphyrins Comprising Three Pyrrole Rings. *Chem. Rev.* **2017**, *117*, 2730−2784. (b) Ahmad, S.; Alam, O.; Naim, M. J.; Shaquiquzzaman, M.; Alam, M.; Iqbal, M. Pyrrole: An insight into recent pharmacological advances with structure activity relationship. *Eur. J. Med. Chem.* **2018**, *157*, 527−561. (c) Jiang, X.; Yue, S.; Chen, K.; Shao, Z.; Li, C.; Su, Y.; Zhao, J. Synthesis, properties and application of novel 5,6,5,6-tetracyclic pyrazine/pyrrole-fused unsymmetric bis(BF_2) fluorescent dyes: BOPYPYs. *Chin. Chem. Lett.* **2019**, *30*, 2271−2273. (d) Najari, A.; Beaupre, S.; Berrouard, P.; Zou, Y.; Pouliot, J. R.; Lepage-Perusse, C.; Leclerc, M. Synthesis and Characterization of New Thieno[3,4-c]pyrrole-4,6-dione Derivatives for Photovoltaic Applications. *Adv. Funct. Mater.* **2011**, *21*, 718−728.

(2) (a) Knorr, L. Ber. Synthese von Furfuranderivaten aus dem Diacetbernsteinsäureester. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2863−2870. (b) Paal, C. Ber. Ueber die Derivate des Acetophenonacetessigesters und des Acetonylacetessigesters. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2756−2767. (c) Balakrishna, A.; Aguiar, A.; Sobral, P. J. M.; Wani, M. Y.; Silva, J. A.; Sobra, A. J. F. N. Paal-Knorr synthesis of pyrroles: from conventional to green synthesis. *Catal. Rev.: Sci. Eng.* **2019**, *61*, 84−110. (d) Kornienko, A.; La Clair, J. J. Covalent modification of biological targets with natural products through Paal−Knorr pyrrole formation. *Nat. Prod. Rep.* **2017**, *34*, 1051−1060.

(3) (a) Knorr, L. Synthetische Versuche mit dem Acetessigester. II. Mittheilung: Ueberführung des Diacetbernsteinsäureesters und des Acetessigesters in Pyrrolderivate. *Justus Liebigs Ann. Chem.* **1886**, *236*, 290. (b) Knorr, L.; Lange, H. Ber. Ueber die Bildung von Pyrrolderivaten aus Isonitrosoketonen. *Ber. Dtsch. Chem. Ges.* **1902**, *35*, 2998−3008.

(4) (a) Hantzsch, A. Ber. Neue Bildungsweise von Pyrrolderivaten. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474. (b) Estévez, V.; Villacampa, M.; Menéndez, J. C. Three-component access to pyrroles promoted by the CAN-silver nitrate system under high-speed vibration milling conditions: a generalization of the Hantzsch pyrrole synthesis. *Chem. Commun.* **2013**, *49*, 591−593.

(5) (a) Estévez, V.; Villacampa, M.; Menéndez, J. C. Recent advances in the synthesis of pyrroles by multicomponent reactions. *Chem. Soc. Rev.* **2014**, *43*, 4633−4657. (b) Zhou, Y.; Zhou, L.; Jesikiewicz, L. T.; Liu, P.; Buchwald, S. L. Synthesis of Pyrroles through the CuH-Catalyzed Coupling of Enynes and Nitriles. *J. Am. Chem. Soc.* **2020**, *142*, 9908−9914. (c) Xiao, P.; Yuan, H.; Liu, J.; Zheng, Y.; Bi, X.; Zhang, J. Radical Mechanism of Isocyanide-Alkyne Cycloaddition by Multicatalysis of Ag_2CO_3, Solvent, and Substrate. *ACS Catal.* **2015**, *5*, 6177−6184. (d) Li, J.-K.; Zhou, B.; Tian, Y.-C.; Jia, C.; Xue, X.-S.; Zhang, F.-G.; Ma, J.-A. Potassium Acetate-Catalyzed Double Decarboxylative Transannulation To Access Highly Functionalized Pyrroles. *Org. Lett.* **2020**, *22*, 9585−9590. (e) Cheng, B.-Y.; Wang, Y.-N.; Li, T.-R.; Lu, L.-Q.; Xiao, W.-J. Synthesis of Polysubstituted Pyrroles through a Formal [4 + 1] Cycloaddition/E1cb Elimination/Aromatization Sequence of Sulfur Ylides and α,β-Unsaturated Imines. *J. Org. Chem.* **2017**, *82*, 12134−12140. (f) Gilbert, Z. W.; Hue, R. J.; Tonks, I. A. Catalytic formal [2 + 2+1] synthesis of pyrroles from alkynes and diazenes via Ti^{II}/Ti^{IV} redox catalysis. *Nat. Chem.* **2016**, *8*, 63−68. (g) Liu, Y.; Parodi, A.; Battaglioli, S.; Monari, M.; Protti, S.; Bandini, M. Visible-Light-Driven Synthesis of 1,3,4-Trisubstituted Pyrroles from Aryl Azides. *Org. Lett.* **2019**, *21*, 7782−7786.

(6) Stuart, D. R.; Alsabeh, P.; Kuhn, M.; Fagnou, K. Rhodium(III)-Catalyzed Arene and Alkene C-H Bond Functionalization Leading to Indoles and Pyrroles. *J. Am. Chem. Soc.* **2010**, *132*, 18326−18339.

(7) Shi, Z.; Suri, M.; Glorius, F. Aerobic Synthesis of Pyrroles and Dihydropyrroles from Imines: Palladium(II)-Catalyzed Intramolecular C-H Dehydrogenative Cyclization. *Angew. Chem., Int. Ed.* **2013**, *52*, 4892−4896.

(8) Lian, Y.; Huber, T.; Hesp, K. D.; Bergman, R. G.; Ellmann, J. A. Rhodium(III)-Catalyzed Alkenyl C-H Bond Functionalization: Convergent Synthesis of Furans and Pyrroles. *Angew. Chem., Int. Ed.* **2013**, *52*, 629−633.

(9) (a) Kumar, P.; Kapur, M. Catalyst Control in Positional-Selective C-H Alkenylation of Isoxazoles and a Ruthenium-Mediated Assembly of Trisubstituted Pyrroles. *Org. Lett.* **2019**, *21*, 2134−2138. (b) Zheng, J.; Huang, L.; Huang, C.; Wu, W.; Jiang, H. Synthesis of Polysubstituted Pyrroles via Pd-Catalyzed Oxidative Alkene C-H Bond Arylation and Amination. *J. Org. Chem.* **2015**, *80*, 1235−1242. (c) Yang, W.; Liu, X.; Leung, P.-H.; Li, Y.; Yang, D.; Chen, Y. Iron-Mediated Ring-Opening and Rearrangement Cascade Synthesis of Polysubstituted Pyrroles from 4-Alkenylisoxazoles. *Adv. Synth. Catal.* **2020**, *362*, 1868−1876.

(10) (a) Rakshit, S.; Patureau, F. W.; Glorius, F. Pyrrole Synthesis via Allylic sp^3 C-H Activation of Enamines Followed by Intermolecular Coupling with Unactivated Alkynes. *J. Am. Chem. Soc.* **2010**, *132*, 9585−9587. (b) Ke, J.; He, C.; Liu, H.; Li, M.; Lei, A. Oxidative cross-coupling/cyclization to build polysubstituted pyrroles from terminal alkynes and β-enamino esters. *Chem. Commun.* **2013**, *49*, 7549−7551. (c) Yan, R.-L.; Luo, J.; Wang, C.-X.; Ma, C.-W.; Huang, G.; Liang, Y.-M. Cu (I)-Catalyzed Synthesis of Polysubstituted Pyrroles from Dialkyl Ethylenedicarboxylates and β-Enamino Ketones or Esters in the Presence of O_2. *J. Org. Chem.* **2010**, *75*, 5395−5397.

(11) (a) Liu, P.; Liu, J.-l.; Wang, H.-s.; Pan, Y.-m.; Liang, H.; Chen, Z.-F. Copper-mediated cross-coupling−cyclization-oxidation: a one-pot reaction to construct polysubstituted pyrroles. *Chem. Commun.* **2014**, *50*, 4795−4698. (b) Senadi, G. C.; Hu, W.-P.; Garkhedkar, A. M.; Boominathan, S. S. K.; Wang, J.-J. Palladium(II)-catalysed regioselective synthesis of 3,4-disubstituted quinolines and 2,3,5-trisubstituted pyrroles from alkenes via anti-Markovnikov selectivity. *Chem. Commun.* **2015**, *51*, 13795−13798. (c) Chen, J.; Chang, D.; Xiao, F.; Deng, G.-J. Three-Component Ordered Annulation of Amines, Ketones, and Nitrovinylarenes: Access to Fused Pyrroles and Substituted Indoles under Metal-Free Conditions. *J. Org. Chem.* **2019**, *84*, 568−578.

(12) (a) Luo, K.; Mao, S.; He, K.; Yu, X.; Pan, J.; Lin, J.; Shao, Z.; Jin, Y. Highly Regioselective Synthesis of Multisubstituted Pyrroles via Ag-Catalyzed $[4 + 1C]^{insert}$ Cascade. *ACS Catal.* **2020**, *10*, 3733−

3740. (b) Li, M.; Sun, Y.; Xie, Y.; Yu, Y.; Huang, F.; Huang, H. Copper-catalyzed carbene insertion and ester migration for the synthesis of polysubstituted pyrroles. *Chem. Commun.* **2020**, *56*, 11050−11053.

(13) (a) Yugandar, S.; Konda, S.; Ila, H. Amine Directed Pd(II)-Catalyzed C-H Activation-Intramolecular Amination of N-Het(aryl)/Acyl Enaminonitriles and Enaminones: An Approach towards Multisubstituted Indoles and Heterofused Pyrroles. *J. Org. Chem.* **2016**, *81*, 2035−2052. (b) Li, X.; Chen, M.; Xie, X.; Sun, N.; Li, S.; Liu, Y. Synthesis of Multiple-Substituted Pyrroles via Gold(I)-Catalyzed Hydroamination/Cyclization Cascade. *Org. Lett.* **2015**, *17*, 2984−2987. (c) Golantsov, N. E.; Golubenkova, A. S.; Festa, A. A.; Varlamov, A. V.; Voskressensky, L. G. A Domino Route toward Polysubstituted Pyrroles from 2-Imidazolines and Electron-Deficient Alkynes. *Org. Lett.* **2020**, *22*, 4726−4731.

(14) For selected reviews and examples, see: (a) Manikandan, R.; Jeganmohan, M. Recent advances in the ruthenium(II)-catalyzed chelation-assisted C-H olefination of substituted aromatics, alkenes and heteroaromatics with alkenes via the deprotonation pathway. *Chem. Commun.* **2017**, *53*, 8931−8947. (b) Tian, S.; Luo, T.; Zhu, Y.; Wan, J.-P. Recent advances in the diversification of chromones and flavones by direct C-H bond activation or functionalization. *Chin. Chem. Lett.* **2020**, *31*, 3073−3082. (c) Zhang, Z.; Tanaka, K.; Yu, J.-Q. Remote site-selective C-H activation directed by a catalytic bifunctional template. *Nature* **2017**, *543*, 538−542. (d) Grimster, N. P.; Gauntlett, C.; Godfrey, C. R. A.; Gaunt, M. J Palladium-Catalyzed Intermolecular Alkenylation of Indoles by Solvent-Controlled Regioselective C-H Functionalization. *Angew. Chem., Int. Ed.* **2005**, *44*, 3125−3129. (e) Cho, S. H.; Hwang, S. J.; Chang, S. Palladium-Catalyzed C-H Functionalization of Pyridine N-Oxides: Highly Selective Alkenylation and Direct Arylation with Unactivated Arenes. *J. Am. Chem. Soc.* **2008**, *130*, 9254−9256. (f) Fu, L.; Xu, Z.; Wan, J.-P.; Liu, Y. The Domino Chromone Annulation and a Transient Halogenation-Mediated C-H Alkenylation toward 3-Vinyl Chromones. *Org. Lett.* **2020**, *22*, 9518−9523.

(15) For reviews, see: (a) Li, X.-B.; Xin, Z.-K.; Xia, S.-G.; Gao, X.-Y.; Tung, C.-H.; Wu, L.-Z. Semiconductor nanocrystals for small molecule activation via artificial photosynthesis. *Chem. Soc. Rev.* **2020**, *49*, 9028−9056. (b) Wang, H.; Gao, X.; Lv, Z.; Abdelilah, T.; Lei, A. Recent Advances in Oxidative R^1-H/R^2-H Cross-Coupling with Hydrogen Evolution via Photo-/Electrochemistry. *Chem. Rev.* **2019**, *119*, 6769−6787. (c) Liu, Q.; Wu, L. Recent advances in visible-light-driven organic reactions. *Nat. Sci. Rev.* **2017**, *4*, 359−380.

(16) (a) Michlik, S.; Kempe, R. A sustainable catalytic pyrrole synthesis. *Nat. Chem.* **2013**, *5*, 140−144. (b) Daw, P.; Chakraborty, S.; Garg, J. A.; Ben-David, Y.; Milstein, D. Direct Synthesis of Pyrroles by Dehydrogenative Coupling of Diols and Amines Catalyzed by Cobalt Pincer Complexes. *Angew. Chem., Int. Ed.* **2016**, *55*, 14373−14377. (c) Zhang, M.; Fang, X.; Neumann, H.; Beller, M. General and Regioselective Synthesis of Pyrroles via Ruthenium-Catalyzed Multicomponent Reactions. *J. Am. Chem. Soc.* **2013**, *135*, 11384−11388. (d) Srimani, D.; Ben-David, Y.; Milstein, D. Direct Synthesis of Pyrroles by Dehydrogenative Coupling of β-Aminoalcohols with Secondary Alcohols Catalyzed by Ruthenium Pincer Complexes. *Angew. Chem., Int. Ed.* **2013**, *52*, 4012−4015. (e) Qu, S.; Dang, Y.; Song, C.; Wen, M.; Huang, K.-W.; Wang, Z.-X. Catalytic Mechanisms of Direct Pyrrole Synthesis via Dehydrogenative Coupling Mediated by PNP-Ir or PNN-Ru Pincer Complexes: Crucial Role of Proton-Transfer Shuttles in the PNP-Ir System. *J. Am. Chem. Soc.* **2014**, *136*, 4974−4991.

(17) (a) Yu, Q.; Liu, Y.; Wan, J.-P. Transition metal-free synthesis of 3-trifluoromethyl chromones via tandem C-H trifluoromethylation and chromone annulation of enaminones. *Org. Chem. Front.* **2020**, *7*, 2770−2775. (b) Zhang, B.; Liu, D.; Sun, Y.; Zhang, Y.; Feng, J.; Yu, F. Preparation of Thiazole-2-thiones through TBPB-Promoted Oxidative Cascade Cyclization of Enaminones with Elemental Sulfur. *Org. Lett.* **2021**, *23*, 3076. (c) Chandran, R.; Pise, A.; Shah, S. K.; Rahul, D.; Suman, V.; Tiwari, N. Copper-Catalyzed Thiolation of Terminal Alkynes Employing Thiocyanate as the Sulfur Source Leading to Enaminone-Based Alkynyl Sulfides under Ambient Conditions. *Org. Lett.* **2020**, *22*, 6557−6561. (d) Wang, F.; Sun, W.; Wang, Y.; Jiang, Y.; Loh, T.-P. Highly Site-Selective Metal-Free C-H Acyloxylation of Stable Enamines. *Org. Lett.* **2018**, *20*, 1256−1260. (e) Yuan, Y.; Hou, W.; Zhang-Negrerie, D.; Zhao, K.; Du, Y. Direct Oxidative Coupling of Enamines and Electron-Deficient Amines: TBAI/TBHP-Mediated Synthesis of Substituted Diaminoalkenes under Metal-Free Conditions. *Org. Lett.* **2014**, *16*, 5410−5413. (f) Mkrtchyan, S.; Iaroshenko, V. O. Visible-light-mediated arylation of ortho-hydroxyarylenaminones: direct access to isoflavones. *Chem. Commun.* **2020**, *56*, 2606−2609. (g) Bagle, P. N.; Mane, M. V.; Sancheti, S. P.; Gade, A. B.; Shaikh, S. R.; Baik, M.-H.; Patil, N. T. Gold(I)-Catalyzed Hydroxy Group Assisted C(sp^2)-H Alkylation of Enaminones with Diazo Compounds to Access 3-Alkyl Chromones. *Org. Lett.* **2019**, *21*, 335−339.

(18) (a) Gu, Z.-Y.; Zhu, T.-H.; Cao, J.-J.; Xu, X.-P.; Wang, S.-Y.; Ji, S.-J. Palladium-Catalyzed Cascade Reactions of Isocyanides with Enaminones: Synthesis of 4-Aminoquinoline Derivatives. *ACS Catal.* **2014**, *4*, 49−52. (b) Hu, D.; Yang, L.; Wan, J.-P. Biaryl and atropisomeric biaryl aldehyde synthesis by one-step, metal-free benzannulation of aryl enals and propiolates. *Green Chem.* **2020**, *22*, 6773−6777. (c) Yang, L.; Wan, J.-P. Ethyl lactate-involved three-component dehydrogenative reactions: biomass feedstock in diversity-oriented quinoline synthesis. *Green Chem.* **2020**, *22*, 3074−3078. (d) Zhao, M.-N.; Ren, Z.-H.; Yang, D.-S.; Guan, Z.-H. Iron-Catalyzed Radical Cycloaddition of 2H-Azirines and Enamides for the Synthesis of Pyrroles. *Org. Lett.* **2018**, *20*, 1287−1290. (e) Jiang, B.; Li, Q.-Y.; Tu, S.-J.; Li, G. Three-Component Domino Reactions for Selective Formation of Indeno[1,2-b]indole Derivatives. *Org. Lett.* **2012**, *14*, 5210−5213. (f) Zhang, F.; Qin, Z.; Kong, K.; Zhao, Y.; Liu, Y.; Li, Y. Metal/Benzoyl Peroxide (BPO)-Controlled Chemoselective Cycloisomerization of (o-Alkynyl)phenyl Enaminones: Synthesis of α-Naphthylamines and Indeno[1,2-c]pyrrolones. *Org. Lett.* **2016**, *18*, 5150−5153.

(19) CCDC 2076610 contains the crystallographic data for **3ag**.

(20) (a) Sun, M.; Chen, W.; Xia, X.; Shen, G.; Ma, Y.; Yang, J.; Ding, H.; Wang, Z. Palladium-Catalyzed Tandem Dehydrogenative [4 + 2] Annulation of Terminal Olefins with N-Sulfonyl Amides via C-H Activations. *Org. Lett.* **2020**, *22*, 3229−3233. (b) Chen, S.-Y.; Sahoo, S. K.; Huang, C.-L.; Chan, T.-H.; Cheng, Y.-J. Pd(II)-Catalyzed Direct Dehydrogenative Mono- and Diolefination of Selenophenes. *Org. Lett.* **2020**, *22*, 2318−2322. (c) Chen, Y.-H.; Shao, N.-Q.; Li, C.; Wang, D.-H. Synthesis of NH-Free 1,4-Dihydroisoquinoline-3(2H)-ones via Pd-Catalyzed C-H Olefination Using Polyfluorosulfinyl as the Auxiliary Group. *Org. Lett.* **2020**, *22*, 5880−5884. (d) Dou, Y.; Kenry; Liu, J.; Jiang, J.; Zhu, Q. Late-Stage Direct *o*-Alkenylation of Phenols by Pd^{II}-Catalyzed C-H Functionalization. *Chem. - Eur. J.* **2019**, *25*, 6896−6901. (e) Richa; Kumar, R.; Zhang, X.; Su, W. Direct remote δ-C(sp^2)-H olefination of β-aryl-substituted aliphatic aldehydes via palladium/enamine co-catalysis. *Org. Chem. Front.* **2020**, *7*, 2965−2974. (f) Manna, M. K.; Hossian, A.; Jana, R. Merging C-H Activation and Alkene Difunctionalization at Room Temperature: A Palladium-Catalyzed Divergent Synthesis of Indoles and Indolines. *Org. Lett.* **2015**, *17*, 672−675.