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Pd-Catalyzed Decarboxylative Cyclization of Trifluoromethyl Vinyl Benzoxazinanones with Sulfur Ylides: Access to Trifluoromethyl Dihydroquinolines

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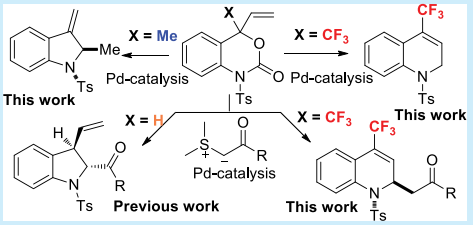
Supporting Information

ABSTRACT: An unprecedented Pd-catalyzed decarboxylative cyclization of 4-trifluoromethyl-4-vinyl benzoxazinanones (**4**) with sulfur ylides (**2**) is reported. While the reactions of 4-vinyl/4-CF_3 benzoxazinanones (**1a**/**1c**) with **2** furnished the 3-vinyl/3-CF_3 indolines (**3a**/**3c**), via an attack on the C_1 carbon of the π-allyl/benzyl zwitterionic intermediates, **4** was converted into 4-trifluoromethyl-dihydroquinolines (**5**) in good yields via an attack on the C_3 carbon of the π-allyl intermediate. The corresponding methyl-substituted analogues afford different products via an attack on the C_2 carbon.



The generation of a variety of functionalized heterocyclic compounds has been a long-standing objective within pharmaceutical companies, given that such compounds represent pharmacophores that are ubiquitous in many naturally occurring biologically active compounds.[1] During the past few years, 4-vinyl benzoxazinanone (**1a**) has emerged as a powerful and versatile synthon for the generation of multiply substituted medium-sized heterocyclic compounds, which include both structural scaffolds used in the pharmaceutical industry and novel heterocyclic skeletons with potential biological appeal.[2] In the presence of Pd-based catalysts, **1a** is susceptible to decarboxylation, which leads to the generation of a zwitterionic π-allyl Pd-intermediate (**Ia**) that can be trapped by suitable interceptors to furnish highly substituted heterocycles via cycloaddition reactions.[2a] The formation of a variety of heterocyclic skeletons based on this strategy can be effectively achieved by judicious selection of the interceptor.[2] A representative example of a Pd-catalyzed interceptive decarboxylative allylic cycloaddition (IDAC) of benzoxazinanones with sulfur ylides (**2**) to furnish 3-vinyl indoline **3a** via a [4 + 1] cycloaddition has been reported by Xiao and co-workers in 2014 (Figure 1a; X = vinyl).[2d] In 2016, Xiao and co-workers applied this strategy to the Cu-catalyzed reaction between 4-propargyl benzoxazinanone (**1b**) and **2** to give 3-alkynyl indoline (**3b**).[3a]

The propargyl group acts as a trigger for the decarboxylation that forms the zwitterionic Cu-allenylidene intermediate **Ib**, followed by a [4 + 1] cycloaddition (Figure 1a; X = propargyl). This type of cycloaddition reaction using both **1a** and **1b** has been intensively expanded by several research groups in recent years using a diverse variety of interceptors to create a multitude of heterocycles.[2,3] While this type of cycloaddition reaction is believed to require an unsaturated carbon-based functional group at the 4-position to initiate the decarboxylation, we extended the scope in 2018 to the 4-trifluoromethyl (CF_3) substituent.[4] Specifically, 4-CF_3 benzoxazinanone (**1c**)

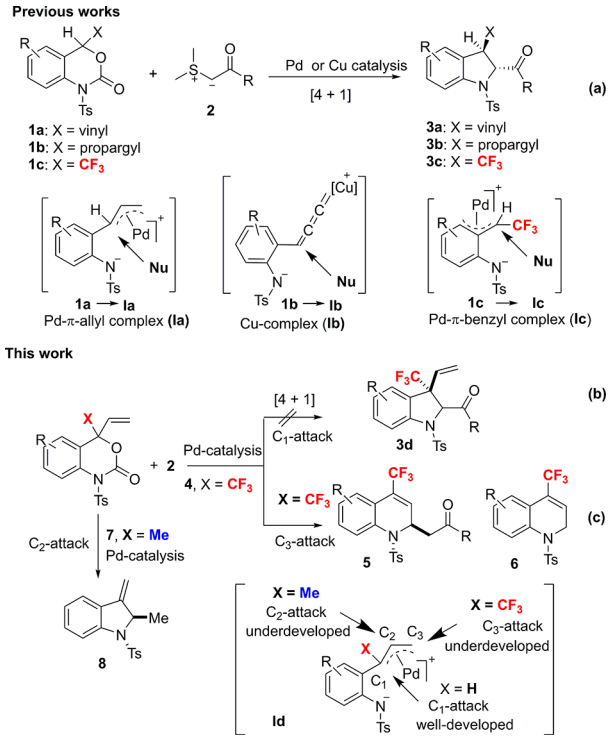


Figure 1. Previous work via C_1 attack (a) and present work via C_2 and C_3 attacks of a π-allyl Pd intermediate (b, c).

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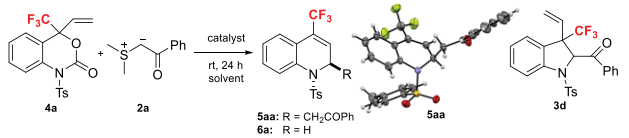
readily reacts with **2** under the similar Pd-catalyzed conditions to provide 3-CF_3-indolines (**3c**) (Figure 1a; X = CF_3).[4a] The highly electrophilic trifluoromethyl-substituted zwitterionic π-benzyl Pd-intermediate **Ic** is proposed for the interceptive decarboxylative benzylic cycloaddition (IDBC) reaction. Independent of the specific reaction pathway (Figure 1a), the nucleophile **2** always attacks at the same benzylic position of **1** (C_1-attack). To further expand this strategy, we were interested in 4-trifluoromethyl 4-vinyl benzoxazinanone **4**, which contains a stereogenic tetrasubstituted carbon center. Under Pd-catalyzed conditions, we envisioned that both CF_3 and vinyl moieties should induce the decarboxylative cycloaddition of **4** with **2** to provide the corresponding 3-CF_3-3-vinyl-indolines **3d** via the [4 + 1] cycloaddition. Consequently, the tetrasubstituted carbon center of **4** should be preserved in the indoline products (**3d**) (Figure 1b). However, the obtained results differed significantly from our expectations. We herein report the Pd-catalyzed decarboxylative cyclization of **4** with **2** to afford 2-substituted 4-trifluoromethyl-1,2-dihydroquinolines (**5**) in good to high yield. Moreover, in the absence of **2**, 2-unsubstituted 4-trifluoromethyl-1,2-dihydroquinolines (**6**) were obtained exclusively in high yield (Figure 1c). An unexpected rare terminal C_3-attack rather than the well-established C_1-attack is crucial for this transformation. It should be noted that the corresponding methyl-analogues (**7**) furnished exomethylene indoline (**8**) via a rare intramolecular C_2-attack.[5]

To generate **3d**, we initially attempted the reaction of **4a** with **2a** under the best conditions reported for the reaction of **1c** and **2** to give **3c**,[4a] i.e., 5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$ and 10 mol % PCy_3 in CH_2Cl_2. However, under these conditions, only complex mixtures were obtained (Table 1, entry 1). After

Table 1. Optimization of the Reaction Conditions for the Catalytic Decarboxylative Cyclization of 4a with 2a[a]



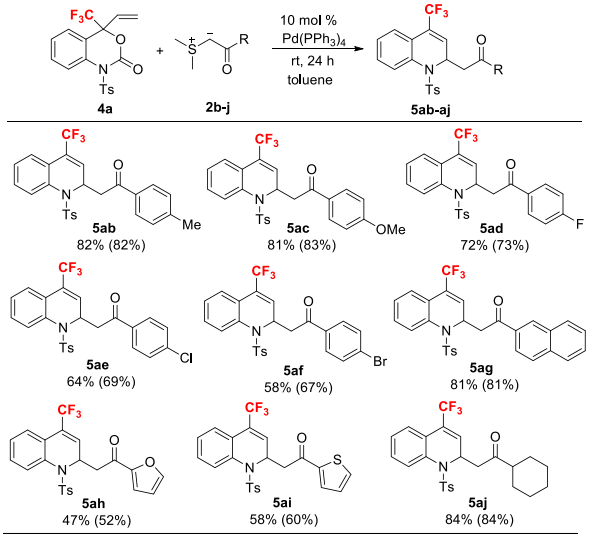
entry	Pd	solvent	ligand	5aa/6a (%)[b]
1	5 mol % $Pd_2(dba)_3{\cdot}CHCl_3$	CH_2Cl_2	10 mol % PCy_3	–
2	10 mol % $Pd(PPh_3)_4$	toluene	–	82/16
3	10 mol % $Pd(PPh_3)_4$	CH_2Cl_2	–	10/70

[a]Experiments were carried out using **4a** (0.15 mmol), **2a** (0.30 mmol), and Pd-source in 1.0 mL of dry solvent. [b]Yields were determined by ^{19}F NMR spectroscopy using $PhCF_3$ as an internal standard.

extensive screening of combinations of palladium sources, solvents, and ligands (Tables S1 and S2), the use of 10 mol % $Pd(PPh_3)_4$ in toluene delivered the unexpected intermolecular reaction product 4-(trifluoromethyl)-1,2-dihydroquinoline derivative (**5aa**) in 82% yield instead of **3d**, together with a small amount of the intramolecular reaction product **6a** (16% yield; entry 2). An X-ray crystallography analysis of **5aa** was carried out to elucidate the solid-state structure of this unexpected dihydroquinoline product (CCDC 1888925). It should be noted that in CH_2Cl_2, under otherwise identical conditions, the intra- vs intermolecular product distribution was reversed, i.e., **6a** was obtained in 70% yield, while **5aa** was generated in 10% yield (entry 3) because of the high solubility of substrates in DCM when compared to toluene.

With the optimal conditions for the formation of **5** in hand, we examined the scope of this reaction by treating **4a** with a variety of sulfur ylides (**2b–j**). As shown in Scheme 1, all ylide

Scheme 1. Scope with Respect to the Sulfur Ylides (2) for the Formation of 5 via Intermolecular Cyclization[a]



[a]Experiments were carried out using **4a** (0.15 mmol), **2b–j** (0.30 mmol), and $Pd(PPh_3)_4$ (0.015 mmol) in 1.0 mL of dry toluene. Isolated yields are shown together with ^{19}F NMR yields using internal standard $PhCF_3$ in parentheses. In all cases, the intramolecular cyclization products (**6a**) were formed in <20% yield.

derivatives were well tolerated under the applied reaction conditions and the corresponding products (**5ab–aj**) were obtained in moderate to good yield (≤84%). Substrates bearing electron-donating groups such as 4-Me (**2b**) and 4-MeO (**2c**) react smoothly to yield the desired products in excellent yield (**5ab**, 82%; **5ac**, 81%). Moreover, compounds containing halogen substituents (**2d**, 4-F; **2e**, 4-Cl; **2f**, 4-Br) were well tolerated and afforded the required CF_3-1,2 dihydroquinolines in moderate to good yield (**5ad**, 72%; **5ae**, 64%; **5af**, 58%). Here, it should be noted that the product yield decreases from 4-F substitution to 4-Br substitution. Heteroaromatic sulfur ylides (**2h**, 2-furyl; **2i**, 2-thiophenyl) smoothly produced the desired products **5ah** and **5ai** in 52% and 60% yield, respectively. Notably, cyclohexyl sulfur ylide **2j** efficiently delivered the corresponding trifluoromethyl 1,2-dihydroquinoline in excellent yield (**5aj**, 84%). In all cases, the intramolecular cyclization product (**6a**) was formed in <20% yield.

Furthermore, we examined the reaction scope with respect to the CF_3-vinyl benzoxazinanones; under the applied reaction conditions, a variety of CF_3-vinyl benzoxazinanone substrates was well tolerated and resulted in the formation of the desired CF_3-1,2-dihydroquinolines in good yield (≤89%) (Scheme 2). For example, methyl-substituted CF_3-vinyl benzoxazinanone **4b** reacted with different sulfur ylides **2** to yield the corresponding products in low to moderate yield (**5ba**, 59%; **5bb**, 65%; **5bd**, 39%), whereas methoxy-substituted **4c** furnished the corresponding products in good yield (**5ca**, 69%; **5cb**, 70%). In addition, substrates bearing chlorine (**4d**) and fluorine (**4e**) substituents smoothly delivered the

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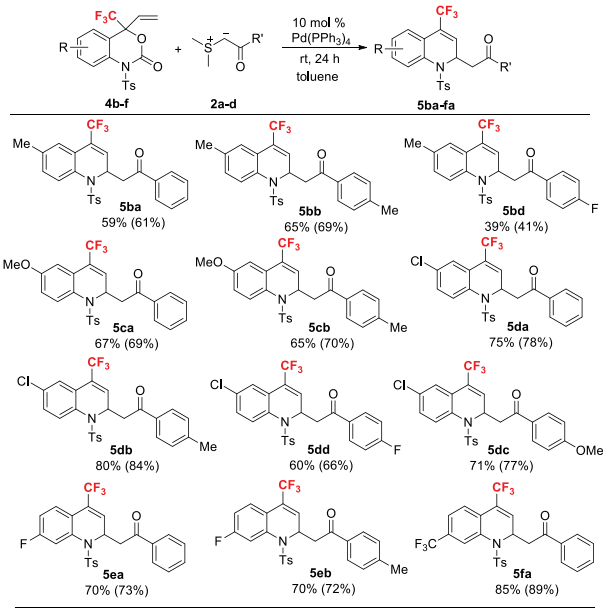
Scheme 2. Scope with Respect to CF_3-Vinyl Benzoxazinanones 4 for the Formation of 5[a]



[a]Experiments were carried out using **4b–f** (0.15 mmol), **2a–d** (0.30 mmol), and $Pd(PPh_3)_4$ (0.015 mmol) in 1.0 mL of dry toluene. Isolated yields are shown together with ^{19}F NMR yields in parentheses. In all cases, <20% of the intramolecular cyclization products (**6**) were observed.

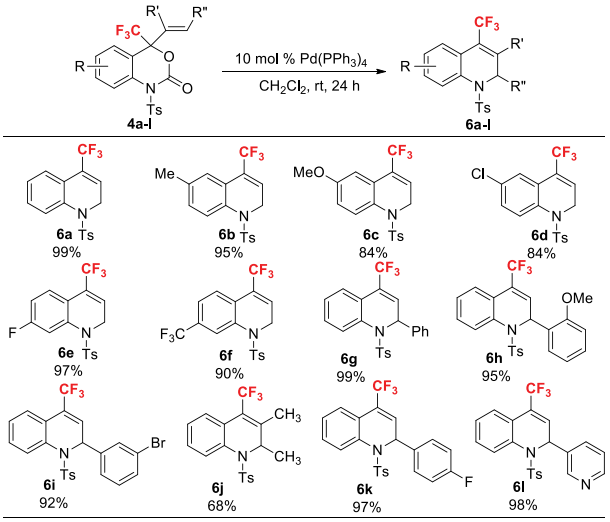
corresponding CF_3-1,2-dihydroquinolines in good yields (**5da**, 75%; **5db**, 80%; **5dc**, 71%; **5ea**, 70%). Compound **4f**, which contains an electron-withdrawing group (CF_3) on the benzene ring, was also well tolerated and afforded **5fa** in excellent yield.

Subsequently, we turned our attention to the synthesis of intramolecular cyclization products **6**. Based on the results obtained in Table 1 (entry 3), we used 10 mol % $Pd(PPh_3)_4$ in CH_2Cl_2 in the absence of ylides for this transformation (Scheme 3). As revealed in Scheme 3, CF_3-vinyl benzoxazinanones **4a–c**, which contain electron-donating substituents on the benzene ring (**4b**, Me; **4c**, MeO) afforded the intramolecular cyclization products in excellent yield (**6a**, 99%; **6b**, 95%; **6c**, 84%) under these reaction conditions. Similarly, CF_3-vinyl benzoxazinanones with electron-withdrawing and halogen substituents (**4f**, CF_3; **4d**, Cl; **4e**, F) delivered the targeted products in good to excellent yield (**6f**, 90%; **6d**, 84%; **6e**, 97%). A variation of the vinyl group in CF_3-vinyl benzoxazinanones **4g–l** also gave the corresponding products in good to high yield (**6g**, 99%; **6h**, 95%; **6i**, 92%; **6j**, 68%; **6k**, 97%). It is noteworthy that pyridine-containing **4l** afforded CF_3-1,2-dihydroquinoline **6l** in 98% yield.

To demonstrate the synthetic utility of the products, we performed a couple of subsequent transformations as outlined in Scheme 4. Intramolecular and intermolecular cyclization reactions can be performed on the gram scale, and **5aa** was successfully reduced with $NaBH_4$ to afford alcohol **9** in 90% yield. The reaction of **6g** with Mg in methanol resulted in the formation of trifluoromethyl-substituted quinoline **10** in 93% yield.

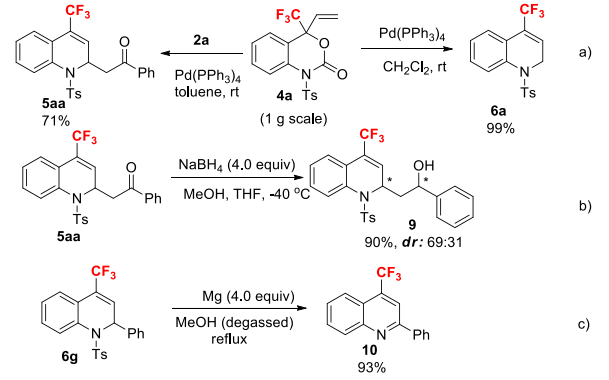
To understand the effect of the CF_3 group on these transformations, we carried out the same reactions using 4-methyl-4-vinyl benzoxazinanones **7** instead of CF_3-substrate **4a**. The reaction of **7a** with sulfur ylide **2a** under the standard

Scheme 3. Scope of CF_3-Vinyl Benzoxazinanones 4 for the Intramolecular Cyclization To Form 6[a]



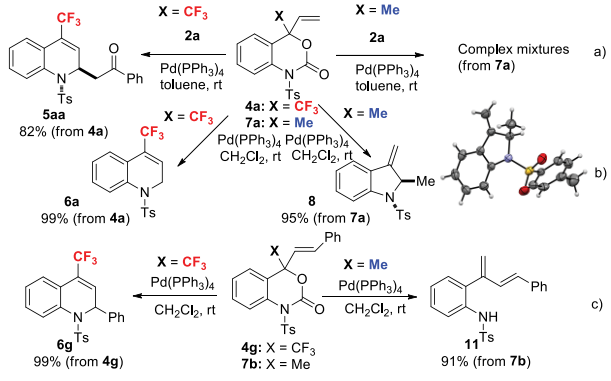
[a]Experiments were carried out using **4a–l** (0.15 mmol) and $Pd(PPh_3)_4$ (0.015 mmol) in 1.0 mL of dry DCM. Yield percentages refer to the isolated yield.

Scheme 4. Subsequent Transformations of 5aa and 6g To Demonstrate the Synthetic Utility of this Method



conditions resulted in the formation of complex mixtures, while **4a** furnished **5aa** in 82% yield (Scheme 5a). Surprisingly, the Pd-catalyzed intramolecular reaction of **7a** in the absence

Scheme 5. Comparison of the Reaction Products Using Methyl-Substituted Benzoxazinanones (7) Instead of CF_3-Benzoxazinanones (4) under Otherwise Identical Reaction Conditions



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of sulfur ylide **2** proceeded differently and generated 2-methyl-3-methylene-1-tosylindoline (**8**) in 95% yield (CCDC 1889136), while **4a** was converted into **6a** (Scheme 5b). Moreover, 4-methyl-4-vinyl benzoxazinanone **7b**, which contains a styryl moiety, afforded the conjugated diene product **11** in 91% yield, while CF_3-analogue **4g** was transformed into **6g** (Scheme 5c).

Based on the obtained results in their entirety, we propose a plausible mechanism for this reaction in Figure 2a. Initially, Pd-

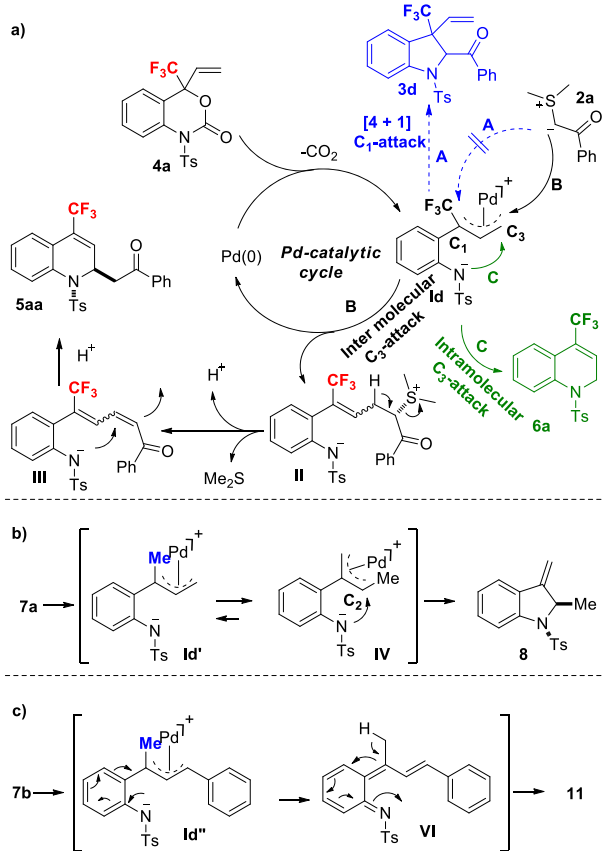

Figure 2. Proposed reaction mechanism.

π-allyl zwitterionic intermediate **Id** could be formed by an oxidative addition of the Pd(0) catalyst to the substrate **4a**. Consistent with previous reports,[2d,4a] sulfur ylide **2a** could then attack at the reactive allylic/benzylic C_1 position, which would be followed by an intramolecular [4 + 1] IDAC or IDBC reaction to give the 3-allyl-3-trifluoromethyl indoline **3d** (path A). However, due to the steric hindrance of the CF_3 moiety in **4a**, **2a** could also attack at the terminal C_3 position of the zwitterionic intermediate **Id**, which would lead to intermediate **II** (path B).[6] Upon elimination of the Me_2S moiety, intermediate **III** could be generated, which could undergo an intramolecular Michael addition to form 1,2-DHQ **5aa**. In the absence of interceptor **2a**, an intramolecular C_3 attack from the nitrogen to the terminal carbon atom would result in the formation of the intramolecular cyclization product **6a** (path C). In the case of **7a**, the zwitterionic π-allyl Pd-intermediate **Id′** would be isomerized to more stable endotype π-allyl Pd-intermediate **IV**, and then the intramolecular cyclization would proceed via a C_2-attack of the nitrogen atom to afford exomethylene indoline **8** (Figure 2b); styryl-substituted **7b** could furnish **11** by an extended conjugated elimination via Pd-polarized aza-*O*-xylylenes **Id″** and **VI** (Figure 2c). Although the electronic effect (CF_3 vs Me) could also be responsible for the change in selectivity (C_1 vs C_3), more investigation including DFT calculation should be required for further discussion.

In conclusion, we have disclosed a unique protocol that delivers biologically attractive 1,2-dihydroquinolines[7] **5** and **6** in good yields from various CF_3-vinyl benzoxazinanones **4** via zwitterionic CF_3-Pd-π-allyl intermediates. Interestingly, the CF_3 group plays a major role to obtain the corresponding dihydroquinolines via a rare C_3-terminal attack of the zwitterionic π-allyl intermediate, whereas previously reported reactions commonly proceed via a C_1 attack. As fluorinated heterocycles represent an important class of drug candidates,[8] the present method can be considered as a useful addition to the synthetic toolkit of medicinal chemists. On the other hand, methyl-substituted benzoxazinanones (**7**) react differently and afford products **8** and **11**. The formation of **8** is also of great importance, given that the reaction should proceed via a rare C_2-attack of the zwitterionic π-allyl intermediate. Details of the reaction mechanism are currently under investigation using DFT calculations, and the results will be reported in due course.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b00330.

Synthesis and NMR spectra (PDF)

Accession Codes

CCDC 1888925 and 1889136 contain 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) Selected books and review: (a) Kunied, T.; Mutsanga, H. The chemistry of heterocyclic compounds. *Palmer (B)* **2002**, 175. (b) Hou, X. L.; Yang, Z.; Wong, H. N. C. *Progress in Heterocyclic Chemistry*; Gribble, G. W., Gilchrist, T., Eds.; Pergamon: Oxford, 2005; Vol. *15*, p 167. (c) Petrov, V. A. *Fluorinated Heterocyclic Compounds: Synthesis, Chemistry, and Applications*; John Wiley & Sons, Inc.: Hoboken, New Jersey, 2009. (d) Katritzky, A.; Ramsden, C.; Joule, J.; Zhdankin, V. *Handbook of Heterocyclic Chemistry*, 3rd ed.; Elsevier: 2010. (e) Eguchi, S. *Bioactive Heterocycles II*; Springer: 2010.

DOI: 10.1021/acs.orglett.9b00330
Org. Lett. XXXX, XXX, XXX−XXX

(f) Pearce, S. The Importance of Heterocyclic Compounds in Anti-Cancer Drug Design. *Therapeutics* **2017**. (g) Martins, M.; Frizzo, C. P.; Moreira, D. N.; Buriol, L.; Machado, P. Solvent-Free Heterocyclic Synthesis. *Chem. Rev.* **2009**, *109*, 4140−4182. (h) Properzi, R.; Marcantoni, E. Construction of heterocyclic structures by trivalent cerium salts promoted bond forming reactions. *Chem. Soc. Rev.* **2014**, *43*, 779−791. (i) Cabrele, C.; Reiser, O. The Modern Face of Synthetic Heterocyclic Chemistry. *J. Org. Chem.* **2016**, *81*, 10109−10125. (j) Heravi, M. M.; Zadsirjan, Z.; Saedi, P.; Momeni, T. Applications of Friedel−Crafts reactions in total synthesis of natural products. *RSC Adv.* **2018**, *8*, 40061−40163. (k) Hudlicky, T. Benefits of Unconventional Methods in the Total Synthesis of Natural Products. *ACS Omega* **2018**, *3*, 17326−17340. (l) Huynh, H. V. Electronic Properties of N-Heterocyclic Carbenes and Their Experimental Determination. *Chem. Rev.* **2018**, *118*, 9457−9492. (m) Swaroop, D. K.; kumar, N. R.; Ratnakarreddy, K.; Raja, G.; Srigiridhar, K.; Poornachandra, Y.; Kumar, C. H.; Babu, N. J.; Kumar, G. S.; Narsaiah, B. Novel 1,2,3-Triazole-Functionalized 1,2-Benzothiazine 1,1-Dioxide Derivatives: Regioselective Synthesis, Biological Evaluation and Docking Studies. *ChemistrySelect* **2018**, *3*, 2398−2403. (n) Tokunaga, E.; Akiyama, H.; Soloshonok, V. A.; Inoue, Y.; Hara, H.; Shibata, N. Biological evaluation of both enantiomers of fluoro-thalidomide using human myeloma cell line H929 and others. *PLoS One* **2017**, *12*, No. e0182152.

(2) (a) Li, T. R.; Wang, Y. N.; Xiao, W. J.; Lu, L. Q. Transition-metal-catalyzed cyclization reactions using vinyl and ethynyl benzoxazinones as dipole precursors. *Tetrahedron Lett.* **2018**, *59*, 1521−1530. (b) Wang, C.; Tunge, J. A. Asymmetric Cycloadditions of Palladium-Polarized Aza-o-xylylenes. *J. Am. Chem. Soc.* **2008**, *130*, 8118−8119. (c) Wang, C.; Pahadi, N.; Tunge, J. A. Decarboxylative Cyclizations and Cycloadditions of Palladium-polarized Aza-ortho-Xylylenes. *Tetrahedron* **2009**, *65*, 5102−5109. (d) Li, T. R.; Tan, F.; Lu, L. Q.; Wei, Y.; Wang, Y. N.; Liu, Y. Y.; Yang, Q. Q.; Chen, J. R.; Shi, D. Q.; Xiao, W. J. Asymmetric trapping of zwitterionic intermediates by sulphur ylides in a palladium-catalysed decarboxylation-cycloaddition sequence. *Nat. Commun.* **2014**, *5*, 5500−5509. (e) Wang, Q.; Qi, X.; Lu, L. Q.; Li, T. R.; Yuan, Z. G.; Zhang, K.; Li, B. J.; Lan, Y.; Xiao, W. Iron-Catalyzed Decarboxylative (4 + 1) Cycloadditions: Exploiting the Reactivity of Ambident Iron-Stabilized Intermediates. *Angew. Chem., Int. Ed.* **2016**, *55*, 2840−2844. (f) Wang, Q.; Li, T. R.; Lu, L. Q.; Li, M. M.; Zhang, K.; Xiao, W. J. Catalytic Asymmetric [4 + 1] Annulation of Sulfur Ylides with Copper−Allenylidene Intermediates. *J. Am. Chem. Soc.* **2016**, *138*, 8360−8363. (g) Wei, Y.; Lu, L. Q.; Li, T. R.; Feng, B.; Wang, Q.; Xiao, W. J.; Alper, H. P,S Ligands for the Asymmetric Construction of Quaternary Stereocenters in Palladium-Catalyzed Decarboxylative [4 + 2] Cycloadditions. *Angew. Chem., Int. Ed.* **2016**, *55*, 2200−2204. (h) Guo, C.; Fleige, M.; Janssen-Muller, D.; Daniliuc, C. G.; Glorius, F. Cooperative N-Heterocyclic Carbene/Palladium-Catalyzed Enantioselective Umpolung Annulations. *J. Am. Chem. Soc.* **2016**, *138*, 7840−7843. (i) Leth, L. A.; Glaus, F.; Meazza, M.; Fu, L.; Thogersen, M. K.; Bitsch, E. A.; Jorgensen, K. A. Decarboxylative [4 + 2] Cycloaddition by Synergistic Palladium and Organocatalysis. *Angew. Chem., Int. Ed.* **2016**, *55*, 15272−15276. (j) Li, M. M.; Wei, Y.; Liu, J.; Chen, H. W.; Lu, L. Q.; Xiao, W. J. Sequential Visible-Light Photoactivation and Palladium Catalysis Enabling Enantioselective [4 + 2] Cycloadditions. *J. Am. Chem. Soc.* **2017**, *139*, 14707−14713. (k) Mei, G. J.; Bian, C. Y.; Li, G. H.; Xu, S. L.; Zheng, W. Q.; Shi, F. Catalytic Asymmetric Construction of the Tryptanthrin Skeleton via an Enantioselective Decarboxylative [4 + 2] Cyclization. *Org. Lett.* **2017**, *19*, 3219−3222. (l) Mei, G. J.; Li, D.; Zhou, G. X.; Shi, Q.; Cao, Z.; Shi, F. A catalytic asymmetric construction of a tetrahydroquinoline-based spirooxindole framework via a diastereo- and enantioselective decarboxylative [4 + 2] cycloaddition. *Chem. Commun.* **2017**, *53*, 10030−10033. (m) Wang, C.; Li, Y.; Wu, Y.; Wang, Q.; Shi, W.; Yuan, C.; Zhou, L.; Xiao, Y.; Guo, H. Asymmetric Synthesis of 3,4-Dihydroquinolin-2-ones via a Stereoselective Palladium-Catalyzed Decarboxylative [4 + 2]- Cycloaddition. *Org. Lett.* **2018**, *20*, 2880−2883. (n) Lu, Y. N.; Lan, J. P.; Mao, Y. J.; Wang, Y. X.; Mei, G. J.; Shi, F. Catalytic asymmetric de novo construction of dihydroquinazolinone scaffolds via enantioselective decarboxylative [4 + 2] cycloadditions. *Chem. Commun.* **2018**, *54*, 13527−13530. (o) Zhao, H. W.; Feng, N. N.; Guo, J. M.; Du, J.; Ding, W. Q.; Wang, L. R.; Song, X. Q. Diastereoselective and Enantioselective Synthesis of Barbiturate-Fused Spirotetrahydroquinolines via Chiral Palladium(0)/Ligand Complex Catalyzed [4 + 2] Cycloaddition of Vinyl Benzoxazinanones with Barbiturate-Based Olefins. *J. Org. Chem.* **2018**, *83*, 9291−9299.

(3) (a) Wang, Q.; Li, T. R.; Lu, L. Q.; Li, M. M.; Zhang, K.; Xiao, W. J. Catalytic Asymmetric [4 + 1] Annulation of Sulfur Ylides with Copper−Allenylidene Intermediates. *J. Am. Chem. Soc.* **2016**, *138*, 8360−8363. (b) Li, T. R.; Cheng, B. Y.; Wang, Y. N.; Zhang, M. M.; Lu, L. Q.; Xiao, W. J. A Copper-Catalyzed Decarboxylative Amination/Hydroamination Sequence: Switchable Synthesis of Functionalized Indoles. *Angew. Chem., Int. Ed.* **2016**, *55*, 12422−12426. (c) Song, J.; Zhang, Z. J.; Gong, L. Z. Asymmetric [4 + 2] Annulation of C1 Ammonium Enolates with Copper-Allenylidenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 5212−5216. (d) Lu, X. H.; Ge, L.; Cheng, C.; Chen, J.; Cao, W. G.; Wu, X. Y. Enantioselective Cascade Reaction for Synthesis of Quinolinones through Synergistic Catalysis Using Cu-Pybox and Chiral Benzotetramisole as Catalysts. *Chem. - Eur. J.* **2017**, *23*, 7689−7693. (e) Shao, W.; You, S. L. Highly Diastereo- and Enantioselective Synthesis of Tetrahydro-5H-Indolo-[2,3-b]quinolines through Copper-Catalyzed Propargylic Dearomatization of Indoles. *Chem. - Eur. J.* **2017**, *23*, 12489−12493. (f) Li, T. R.; Lu, L. Q.; Wang, Y. N.; Wang, B. C.; Xiao, W. J. Divergent Synthesis of Polycyclic Indolines: Copper-Catalyzed Cascade Reactions of Propargylic Carbamates and Indoles. *Org. Lett.* **2017**, *19*, 4098−4101. (g) Lu, Q.; Cembellin, S.; Gressies, S.; Singha, S.; Daniliuc, C. G.; Glorius, F. Manganese(I)-Catalyzed C-H (2-Indolyl)methylation: Expedient Access to Diheteroarylmethanes. *Angew. Chem., Int. Ed.* **2018**, *57*, 1399−1403. (h) Wang, B. C.; Wang, Y. N.; Zhang, M. M.; Xiao, W. J.; Lu, L. Q. Copper-catalyzed decarboxylative cyclization via tandem C−P and C−N bond formation: access to 2-phosphorylmethyl indoles. *Chem. Commun.* **2018**, *54*, 3154−3157. (i) Wang, S.; Liu, M.; Chen, X.; Wang, H.; Zhai, H. Copper-catalyzed decarboxylative propargylation/hydroamination reactions: access to C_3 β-ketoester-functionalized indoles. *Chem. Commun.* **2018**, *54*, 8375−8378. (j) Chen, H.; Lu, X.; Xia, X.; Zhu, Q.; Song, Y.; Chen, J.; Cao, W.; Wu, X. Asymmetric Catalytic [4 + 2] Cycloaddition via Cu−Allenylidene Intermediate: Stereoselective Synthesis of Tetrahydroquinolines Fused with a γ-Lactone Moiety. *Org. Lett.* **2018**, *20*, 1760−1763. (k) Li, T. R.; Zhang, M. M.; Wang, B. C.; Lu, L. Q.; Xiao, W. J. Synthesis of 3,3′-Biindoles through a Copper-Catalyzed Friedel − Crafts Propargylation/Hydroamination/Aromatization Sequence. *Org. Lett.* **2018**, *20*, 3237−3240. (l) Jiang, F.; Feng, X.; Wang, R.; Gao, X.; Jia, H.; Xiao, Y.; Zhang, C.; Guo, H. Asymmetric [3 + 3] Annulation of Copper−Allenylidenes with Pyrazolones: Synthesis of Chiral 1,4-Dihydropyrano[2,3-*c*]pyrazoles. *Org. Lett.* **2018**, *20*, 5278−5281. (m) Wang, Y.; Zhu, L.; Wang, M.; Xiong, J.; Chen, N.; Feng, X.; Xu, Z.; Jiang, X. Catalytic Asymmetric [4 + 3] Annulation of C,N-Cyclic Azomethine Imines with Copper Allenylidenes. *Org. Lett.* **2018**, *20*, 6506−6509.

(4) (a) Punna, N.; Das, P.; Gouverneur, V.; Shibata, N. Highly Diastereoselective Synthesis of Trifluoromethyl Indolines by Interceptive Benzylic Decarboxylative Cycloaddition of Nonvinyl, Trifluoromethyl Benzoxazinanones with Sulfur Ylides under Palladium Catalysis. *Org. Lett.* **2018**, *20*, 1526−1529. (b) Das, P.; Gondo, S.; Punna, N.; Uno, H.; Tokunaga, E.; Shibata, N. Access to benzo-fused nine-membered heterocyclic alkenes with a trifluoromethyl carbinol moiety via a double decarboxylative formal ring-expansion process under palladium catalysis. *Chem. Sci.* **2018**, *9*, 3276−3281. (c) Punna, N.; Harada, K.; Shibata, N. Stille cross-coupling of secondary and tertiary α-(trifluoromethyl)-benzyl chlorides with allylstannanes. *Chem. Commun.* **2018**, *54*, 7171−7174.

(5) (a) Hoffmann, H. M. R.; Otte, A. R.; Wilde, A. Nucleophilic Attack at the Central Carbon Atom of (π-Allyl)palladium Complexes: Formation of α-Cyclopropyl Esters. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 234−235. (b) Wilde, A.; Otte, A. R.; Hoffmann, H. M. R.

DOI: 10.1021/acs.orglett.9b00330
Org. Lett. XXXX, XXX, XXX−XXX

Cyclopropanes via nucleophilic attack at the central carbon of (π-allyl)palladium complexes. *J. Chem. Soc., Chem. Commun.* **1993**, *0*, 615−616. (c) Otte, A. R.; Wilde, A.; Hoffmann, H. M. R. Cyclopropanes by Nucleophilic Attack of Mono-and Diaryl-Substituted (η^3-Allyl)palladium Complexes: Aryl Effect and Stereochemistry. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 1280−1282. (d) Hoffmann, H. M. R.; Otte, A. R.; Wilde, A.; Menzer, S.; Williams, D. J. Isolation and X- Ray Crystal Structure of a Palladacyclobutane: Insight into the Mechanism of Cyclopropanation. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 100−102. (e) Huang, J. Q.; Liu, W.; Zheng, B. H.; Liu, X. Y.; Yang, Z.; Ding, C. H.; Li, H.; Peng, Q.; Hou, X. L. Pd-Catalyzed Asymmetric Cyclopropanation Reaction of Acyclic Amides with Allyl and Polyenyl Carbonates. Experimental and Computational Studies for the Origin of Cyclopropane Formation. *ACS Catal.* **2018**, *8*, 1964−1972.

(6) (a) Hanzawa, Y.; Ishizawa, S.; Kobayashi, Y. Palladium(0)-catalyzed reactions of trifluoromethylated allylic ester derivatives: Synthesis of trifluoromethylated chrysanthemic acid ester. *Chem. Pharm. Bull.* **1988**, *36*, 4209−4212. (b) Iseki, K.; Kuroki, Y.; Nagai, T.; Kobayashi, Y. Preparation of optically active 2-(trifluoromethyl)-alkan-1-ols by catalytic asymmetric hydrogenation. *J. Fluorine Chem.* **1994**, *69*, 5−6. (c) Konno, T.; Ishihara, T.; Yamanaka, H. Highly regio- and stereo-controlled Pd(0)-catalyzed nucleophilic substitution reaction for the synthesis of optically active γ-fluoroalkylated allylic alcohols. *Tetrahedron Lett.* **2000**, *41*, 8467−8472. (d) Konno, T.; Nagata, K.; Ishihara, T.; Yamanaka, H. Concise Syntheses of Nonracemic γ-Fluoroalkylated Allylic Alcohols and Amines Via an Enantiospecific Palladium-Catalyzed Allylic Substitution Reaction. *J. Org. Chem.* **2002**, *67*, 1768−1775. (e) Konno, T.; Takehana, T.; Ishihara, T.; Yamanaka, H. The fluorine-containing π-allylmetal complex. The transition metal-catalyzed allylic substitution reaction of fluorinated allyl mesylates with various carbon nucleophiles. *Org. Biomol. Chem.* **2004**, *2*, 93−98. (f) Kawatsura, M.; Hirakawa, T.; Tanaka, T.; Ikeda, D.; Hayase, S.; Itoh, T. Regioselective synthesis of trifluoromethyl group substituted allylic amines via palladium-catalyzed allylic amination. *Tetrahedron Lett.* **2008**, *49*, 2450−2453. (g) Kawatsura, M.; Terasaki, S.; Minakawa, M.; Hirakawa, T.; Ikeda, K.; Itoh, T. Synthesis of Unsymmetrical *o*-Biphenols and *o*-Binaphthols via Silicon-Tethered Pd-Catalyzed C−H Arylation. *Org. Lett.* **2014**, *16*, 2442−2445. (h) Hemelaere, R.; Desroches, J.; Paquin, J. F. Introduction of the 4,4,4-Trifluorobut-2-ene Chain Exploiting a Regioselective Tsuji−Trost Reaction Catalyzed by Palladium Nanoparticles. *Org. Lett.* **2015**, *17*, 1770−1773.

(7) (a) Tsushima, K.; Hatakoshi, M.; Matsuo, N.; Ohno, N.; Nakayama, I. Synthesis and Anti-juvenile Hormone Activity of 2, 2-Dimethyl-1, 2-dihydroquinoline Derivatives, Nitrogen Analogues of Precocene I and II. *Agric. Biol. Chem.* **1985**, *49*, 2421−2423. (b) Johnson, J. V.; Rauckman, B. S.; Baccanari, D. P.; Roth, B. 2,4-Diamino-5-benzylpyrimidines and analogs as antibacterial agents. 12. 1,2-Dihydroquinolylmethyl analogs with high activity and specificity for bacterial dihydrofolate reductase. *J. Med. Chem.* **1989**, *32*, 1942−1949. (c) He, P.; Ackman, R. G. HPLC determination of ethoxyquin and its major oxidation products in fresh and stored fish meals and fish feeds. *J. Sci. Food Agric.* **2000**, *80*, 10−16. (d) Arseniyadis, S.; Wagner, A.; Mioskowski, C. Resin-bound 4-phenyl-1,2-dihydroquinoline (DHQ): a new safety-catch linker for solid-phase organic synthesis (SPOS). *Tetrahedron Lett.* **2004**, *45*, 2251−2253. (e) Takahashi, H.; Bekkali, Y.; Capolino, A. J.; Gilmore, T.; Goldrick, S. E.; Kaplita, P. V.; Liu, L.; Nelson, R. M.; Terenzio, D.; Wang, J.; Zuvela, J. L.; Proudfoot, J.; Nabozny, G.; Thomson, D. Discovery and SAR study of novel dihydroquinoline-containing glucocorticoid receptor agonists. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 5091−5095. (f) Fotie, J.; Kaiser, M.; Delfín, D. A.; Manley, J.; Reid, C. S.; Paris, J. M.; Wenzler, T.; Maes, L.; Mahasenan, K. V.; Li, C.; Werbovetz, K. A. Antitrypanosomal Activity of 1,2-Dihydroquinolin-6-ols and Their Ester Derivatives. *J. Med. Chem.* **2010**, *53*, 966−982. (g) Sathe, M.; Derveni, M.; Allen, M.; Cullen, D. C. Use of polystyrene-supported 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline for the preparation of a hapten−protein conjugate for antibody development. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 1792−1974. (h) Reid, C. S.; Patrick, D. A.; He, S.; Fotie, J.; Premalatha, K.; Tidwell, R. R.; Wang, M. Z.; Liu, Q.; Gershkovich, P.; Wasan, K. M.; Wenzler, T.; Brun, R.; Werbovetz, K. A. Synthesis and antitrypanosomal evaluation of derivatives of N-benzyl-1,2-dihydroquinolin-6-ols: Effect of core substitutions and salt formation. *Bioorg. Med. Chem.* **2011**, *19*, 513−523. (i) Bandyopadhyay, P.; Sathe, M.; Sharma, P.; Kaushik, M. P. Exploration of polystyrene-supported 2-isobutoxy-1-isobutoxycarbonyl-1,2-dihydroquinoline (PS-IIDQ) as new coupling agent for the synthesis of 8-substituted xanthine derivatives. *Tetrahedron Lett.* **2012**, *53*, 4631−4636.

(8) (a) Ojima, I. *Fluorine in Medicinal Chemistry and Chemical Biology*; Wiley-Blackwell: Chichester, U.K., 2009. (b) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013. (c) Isanbor, C.; O'Hagan, D. Fluorine in medicinal chemistry: A review of anti-cancer agents. *J. Fluorine Chem.* **2006**, *127*, 303−319. (d) Menaa, F.; Menaa, B.; Sharts, O. N. Importance of Fluorine and Fluorocarbons in Medicinal Chemistry and Oncology. *J. Mol. Pharm. Org. Process Res.* **2013**, *1*, 1000104. (e) Kawai, H.; Shibata, N. Asymmetric Synthesis of Agrochemically Attractive Trifluoromethylated Dihydroazoles and Related Compounds under Organocatalysis. *Chem. Rec.* **2014**, *14*, 1024−1040. (f) Wang, J.; Rosello, M. S.; Acena, J. L.; Pozo, C. D.; Sorochinsky, A. E.; Fustero, S.; Soloshonok, V. A.; Liu, H. Fluorine in Pharmaceutical Industry: Fluorine-Containing Drugs Introduced to the Market in the Last Decade (2001−2011). *Chem. Rev.* **2014**, *114*, 2432−2506. (g) *Chemistry: Principles and Commercial Applications*; Plenum: New York, 1994. (h) Ojima, I.; McCarthy, J. R.; Welch, J. T. *Biomedical Frontiers of Fluorine Chemistry*; ACS: Washington, DC, 1996. (i) Hiyama, H.; *Organofluorine Compounds: Chemistry and Applications*; Springer: Berlin, 2000. (j) Kirsch, P.; *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, 2004. (k) Ozoe, Y. Chapter Four - γ-Aminobutyrate- and Glutamate-gated Chloride Channels as Targets of Insecticides. *Adv. Insect Physiol.* **2013**, *44*, 211−286. (l) Xu, X. H.; Matsuzaki, K.; Shibata, N. Synthetic Methods for Compounds Having CF_3−S Units on Carbon by Trifluoromethylation, Trifluoromethylthiolation, Triflylation, and Related Reactions. *Chem. Rev.* **2015**, *115*, 731−764. (m) Vrouenraets, S. M. E.; Wit, F. W. N. M.; Tongeren, J. V.; Lange, J. M. A. Efavirenz: a review. *Expert Opin. Pharmacother.* **2007**, *8*, 851−871. (n) Li, S.; Ma, J. A. Core-structure-inspired asymmetric addition reactions: enantioselective synthesis of dihydrobenzoxazinone- and dihydroquinazolinone-based anti-HIV agents. *Chem. Soc. Rev.* **2015**, *44*, 7439−7448. (o) Gassel, M.; Wolf, C.; Noack, S.; Williams, H.; Ilg, T. The novel isoxazoline ectoparasiticide fluralaner: Selective inhibition of arthropod γ-aminobutyric acid- and L-glutamate-gated chloride channels and insecticidal/acaricidal activity. *Insect Biochem. Mol. Biol.* **2014**, *45*, 111−124. (p) Ozoe, Y. Access to benzo-fused nine-membered heterocyclic alkenes with a trifluoromethyl carbinol moiety via a double decarboxylative formal ring-expansion process under palladium catalysis. *Adv. Insect Physiol.* **2013**, *44*, 211−286.

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Org. Lett. XXXX, XXX, XXX−XXX