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Potassium Acetate-Catalyzed Double Decarboxylative Transannulation To Access Highly Functionalized Pyrroles

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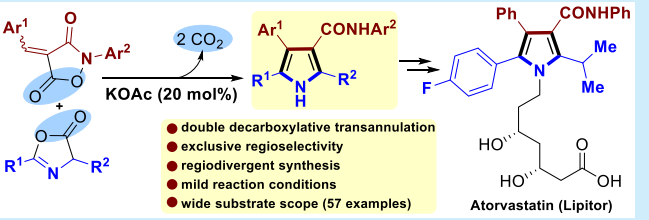
ABSTRACT: The development of new synthetic strategies for the efficient construction of versatile pyrrole pharmacores, especially in an operationally simple and environmentally benign fashion, still remains a momentous yet challenging goal. Here, we report a KOAc-catalyzed double decarboxylative transannulation between readily accessible oxazolones and isoxazolidinediones. This transformation represents a new way for skeletal remodeling by utilizing CO_2 moiety as traceless activating and directing groups in both reaction partners. The synthetic value is evidenced by the rapid preparation of a broad spectrum of highly functionalized 3-carbamoyl-4-aryl pyrroles in good to excellent yields with exclusive regiocontrol, including the important Atorvastatin core.



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Transition-metal catalysis has been among the most vibrant fields in modern synthetic chemistry. Over the past decades, research efforts have mainly focused on many precious transition-metal catalysts.[1] Notably, the lack of long-term sustainability and the toxicity of these noble metals has led to a renewed interest in the development of Earth-abundant base metal species for use in catalysis.[2] Catalysts derived from Earth-abundant base metals undoubtedly offer synthetic chemists more opportunities than we can imagine. In this context, potassium is the sixth-most abundant metal element in the Earth's crust,[3] and traditionally it has been mainly employed as simple alkali-metal bases. Interestingly, the potential of potassium in catalysis and organic synthesis has begun to attract significantly increasing attention in recent years. For example, in a series of pioneering studies, potassium alkoxides have found versatile applications in carbon−carbon and carbon−heteroatom bond-forming reactions, including heteroaromatic C−H silylation,[4] aromatic C−H arylation,[5] heteroaromatic C−H iodination,[6] and alkyne hydrocarboxylation.[7] Despite these remarkable advances, the development of more reaction varieties with potassium catalysts is certainly still of much interest and significance.[8]

Tetra-substituted pyrroles are an important class of *N*-heterocyclic motifs present in many pharmaceutical agents, agrochemical ingredients, and natural products.[9] Several representative compounds include Atorvastatin (a cholesterol-lowering drug),[10] Sunitinib (an anticancer drug),[11] Licofelone (a dual COX/LOX inhibitor),[12] FPL-64176 (a Ca-channel activator),[13] Chlorfenapyr (an agrochemical pesticide),[14] and marine alkaloids Polycitones and Storniamides[15] (Figure 1). Tetra-substituted pyrroles are also found widely in life system (pigment heme, chlorophyll, bacteriochlorin, and porphyrinogen molecules) and functional materials (man-made batteries and solar cells).[16] The broad biological activities and attractive physicochemical properties of tetra-substituted pyrroles, as well as their industrial relevance have long motivated the development of new and practical

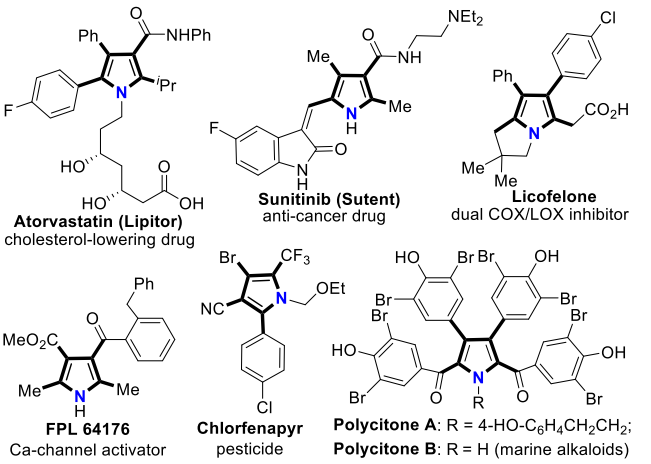

Figure 1. Representative bioactive molecules featuring a tetra-substituted pyrrole motif.

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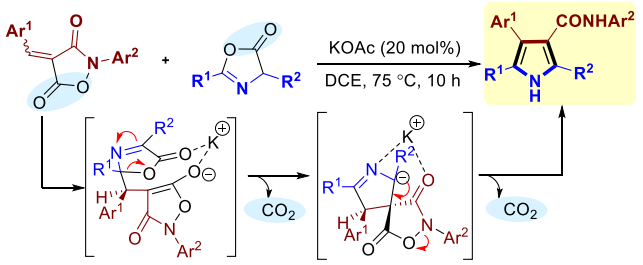
methods for their construction.[17] In particular, the exploitation of novel substrates and strategies under mild conditions with good functional group tolerance is still in high demand. Consistent with our continuing interest in directed cycloaddition reactions,[18] here we report a novel double decarboxylative transannulation process catalyzed by inexpensive and readily available potassium acetate (KOAc) (see Scheme 1).[19] This alkali-metal salt catalyst-triggered trans-

Scheme 1. KOAc-Catalyzed Decarboxylative Transannulation for the Synthesis of Tetrasubstituted NH-Pyrroles

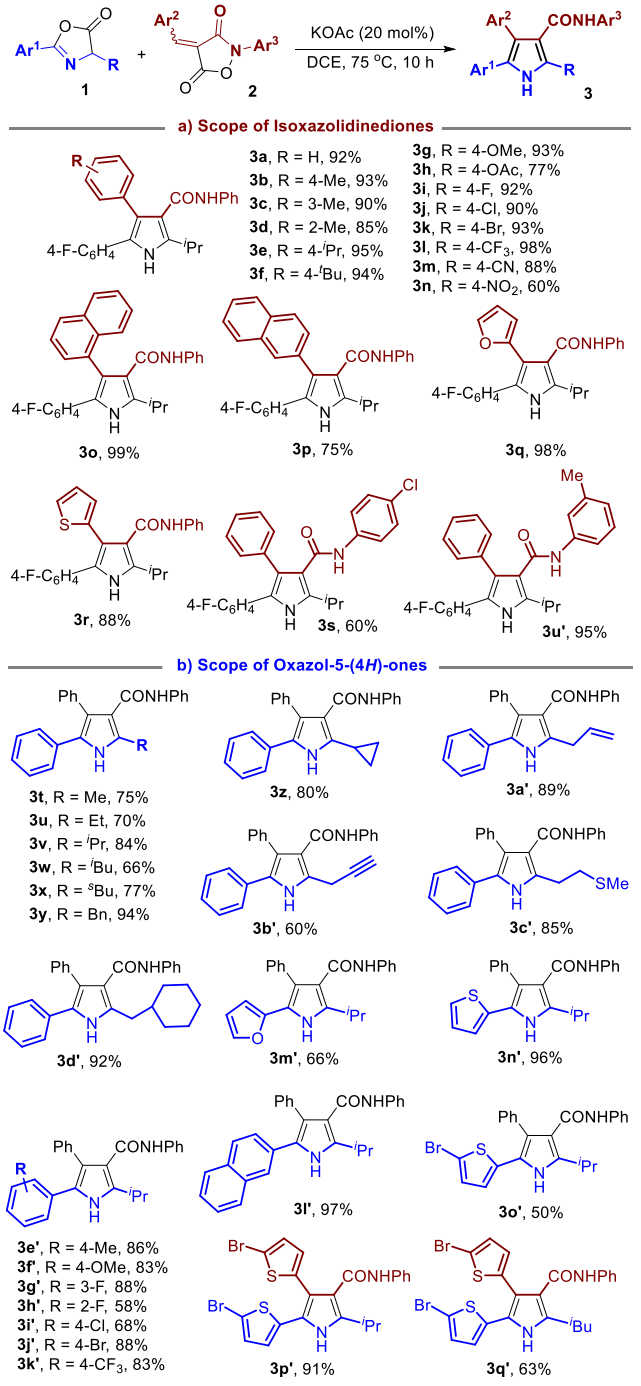


formation of oxazolones and isoxazolidinediones provides an efficient route to a broad range of tetra-substituted 3-carbamoyl-4-aryl NH-pyrroles in good yields and with exclusive regioselectivities. The cleavage of the weak N−O bond in isoxazolidinedione serves as a key in triggering the second decarboxylation and ultimately leads to the formation of the pyrrole ring.

After extensive screening studies, we found that the use of an alkali-metal acetate (KOAc) as a catalyst delivered the desired product **3a** as a single regioisomer in up to 92% yield (see Table S1 in the Supporting Information (SI)). Having established optimal conditions for the KOAc-catalyzed double decarboxylative transannulation reaction, the scope was first assessed with oxazolone **1a** and a series of isoxazolidine-3,5-diones **2** (Scheme 2a). A variety of aromatic substituents (Ar^1) featuring various electronic properties (electron-donating and electron-withdrawing) and located patterns (*para*-, *meta*-, and *ortho*-) are all compatible, thus providing highly functionalized pyrroles **3b**−**3n** in yields of 60%−98% with constantly excellent regioselectivity. Two types of naphthyl-derived substrates, as well as 2-furyl and 2-thienyl ones, also underwent the desired decarboxylative transannulation with uniformly good results (products **3o**−**3r**). A change of substituents on the amide moiety was well-tolerated, as exemplified by the smooth generation of compound **3s** and **3u′**. It is noteworthy that the current catalytic system can tolerate an *E*/*Z* mixture of isoxazolidine-3,5-diones **2**. The ability to transform the *E*/*Z* mixture of **2** is crucial to practical synthesis of various tetrasubstituted NH-pyrroles.

Subsequently, a broad array of oxazolones **1** reacted with isoxazolidinedione **2a** under the optimized conditions, and the results are outlined in Scheme 2b. Various alkyl substituents that include methyl, ethyl, isopropyl, isobutyl, *sec*-butyl, benzyl, cyclopropyl, alkenyl, alkynyl, thioether, and cyclohexyl groups were well accommodated, delivering the products **3t**−**3d′** in yields of 60%−94%. Variations on the aryl units of oxazolones **1** had no significant effect on the reaction performance, including phenyl-derived substrates bearing alkyl, alkoxyl, trifluoromethyl groups or a halogen at different positions (products **3e′**−**3k′**). Reactions of oxazolones containing

Scheme 2. Substrate Scope of (a) Isoxazolidinediones 2 and (b) Oxazol-5-(4*H*)-ones 1



naphthyl or heteroaryl groups also occurred smoothly, producing the corresponding pyrroles **3l′**−**3q′** in up to 97% yield. The bromo-substituted thienyl pyrroles may serve as potential building blocks for the preparation of novel small-molecule optoelectronic materials.[20]

This KOAc-catalyzed double decarboxylative transannulation reaction can further be applied for the expedient preparation of triaryl-substituted pyrroles with excellent regioselectivity. As illustrated in Scheme 3, a series of highly functionalized pyrroles **4a**−**4k** bearing three precisely arranged aryl groups were readily obtained in practical yields as a single detectable regioisomer under operationally simple conditions.

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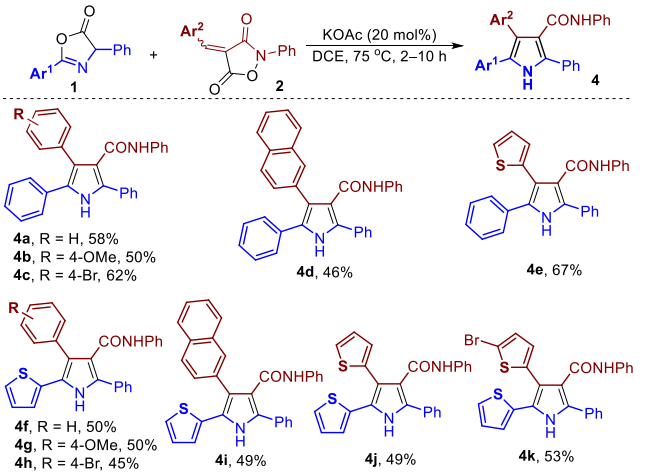
Scheme 3. Synthesis of Tri-aryl-substituted Pyrroles



Note that the regioselective synthesis of such highly substituted pyrroles **4g**−**4k**, possessing three different aryl groups, is otherwise difficult to access.

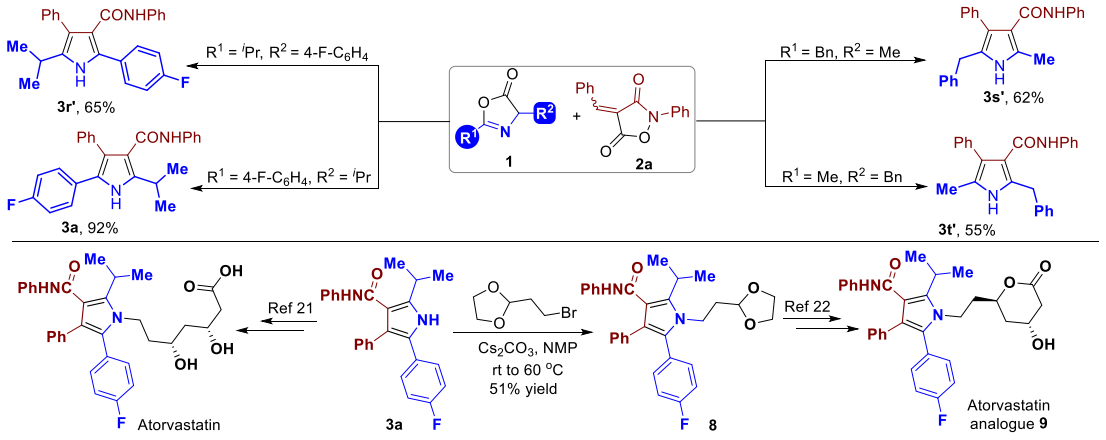
Subsequently, the utility of the present protocol was further highlighted by the regiodivergent construction of pyrroles **3r′**−**3t′** (Scheme 4). By virtue of switching the substituents on the oxazolone motif, the corresponding regioisomer **3r′** (relative to **3a**) was prepared in 65% yield. Similarly, both tetrasubstituted NH-pyrroles **3s′** and **3t′** were obtained as a single regioisomer in yields of 62% and 55%, respectively. The structures of these regioisomers were unambiguously determined by X-ray crystallography analysis of compounds **3a**, **3s′**, and **3t′**. Furthermore, the same good result was obtained when the model transannulation reaction was conducted on a gram scale, thus delivering 3.6 g of **3a** with 89% yield in one pot. Notably, **3a** could function as a very valuable synthon, which was directly converted to the cholesterol-lowering drug Atorvastatin (Scheme 4).[21] In addition, the S_N2 substitution reaction of **3a** with 2-(2-bromoethyl)-1,3-dioxolane gave *N*-alkylated pyrrole **8** in 51% isolation yield, which is a key compound that is a known intermediate in the synthesis of the Atorvastatin analogue **9**.[22]

To gain insight into the reaction mechanism, we initially attempted to perform the transannulation reaction between oxazolone **1a** and two acyclic derivatives of isoxazolidinedione **2a** as potential intermediates (acyclic alkenyl amide **5** and alkynyl amide **6**, respectively). In these two cases, no desired pyrrole **3a** was observed (Scheme 5a). This result not only illustrated the critical role of employing the CO_2 moiety as a traceless activating and directing group in the reaction design, but it also indicated that the first transannulation step could occur prior to the ring-opening event. Monitoring the reaction mixture of oxazolone **1a** with isoxazolidinedione **2a** under standard conditions by ^{19}F NMR and ^{1}H NMR also indicated the in-situ formation of possible intermediate species (see Figures S1 and S2 in the SI). To verify this hypothesis, $TMSCHN_2$ was used to intercept the model reaction when it was conducted at 0 °C in THF. To our delight, a spirocyclic compound **7** was obtained in 25% yield (confirmed by X-ray crystallography analysis; see Scheme 5b), thereby strongly supporting the presence of respective spirocyclic intermediate before decarboxylation during the reaction process.

To further elucidate the origin of excellent regioselectivity in this double decarboxylative transannulation reaction, the density functional theory (DFT) calculations were performed at the SMD (DCE)-M06/6-311++G(d,p)//SMD(DCE)-M06/6-31g(d) level of theory (Scheme 5c). In the favored pathway **I** (in black), the 1,4-nucleophilic attack at the C2 position of isoxazolidinedione **2a** occurred with an energy barrier of 4.2 kcal/mol (via the transition state **endo-Ts-Ia**). Subsequently, spirocyclic intermediate **endo-Int-Ic** was formed after the ring opening via the transition state **endo-Ts-Ib**, then intramolecular addition event via the transition state **endo-Ts-Ic** with energy barriers of 13.4 and 1.8 kcal/mol, respectively. Note that the K^+ cation was found to be simultaneously binding with oxygen of the carbonyl group in both reaction partners from the starting **endo-Ts-Ia** until the formation of intermediate **endo-Int-Ic**. Based on the computed energy profile, the decarboxylation process is estimated to be the rate-determining step with an overall free-energy requirement of 19.8 kcal/mol (from **endo-Int-Ic** to **endo-Ts-Id**). On the other hand, the nucleophilic attack at the C4 position of isoxazolidinedione **1b**, following with the concerted intramolecular addition and ring-opening event involving a single transition state **exo-Ts-IIb**, has a much higher barrier of 29.8 kcal/mol (in the disfavored pathway **II**; shown in red in Scheme 5c). This major difference may account for the preference of pathway **I** over **II**, which is consistent with the experimental outcome that **3t** was exclusively formed.

On the basis of the combined experimental and computational results, a plausible mechanism was deduced as depicted

Scheme 4. Regiodivergent Synthesis of Polysubstituted Pyrroles and Synthesis of Atorvastatin and Its Analogue 9



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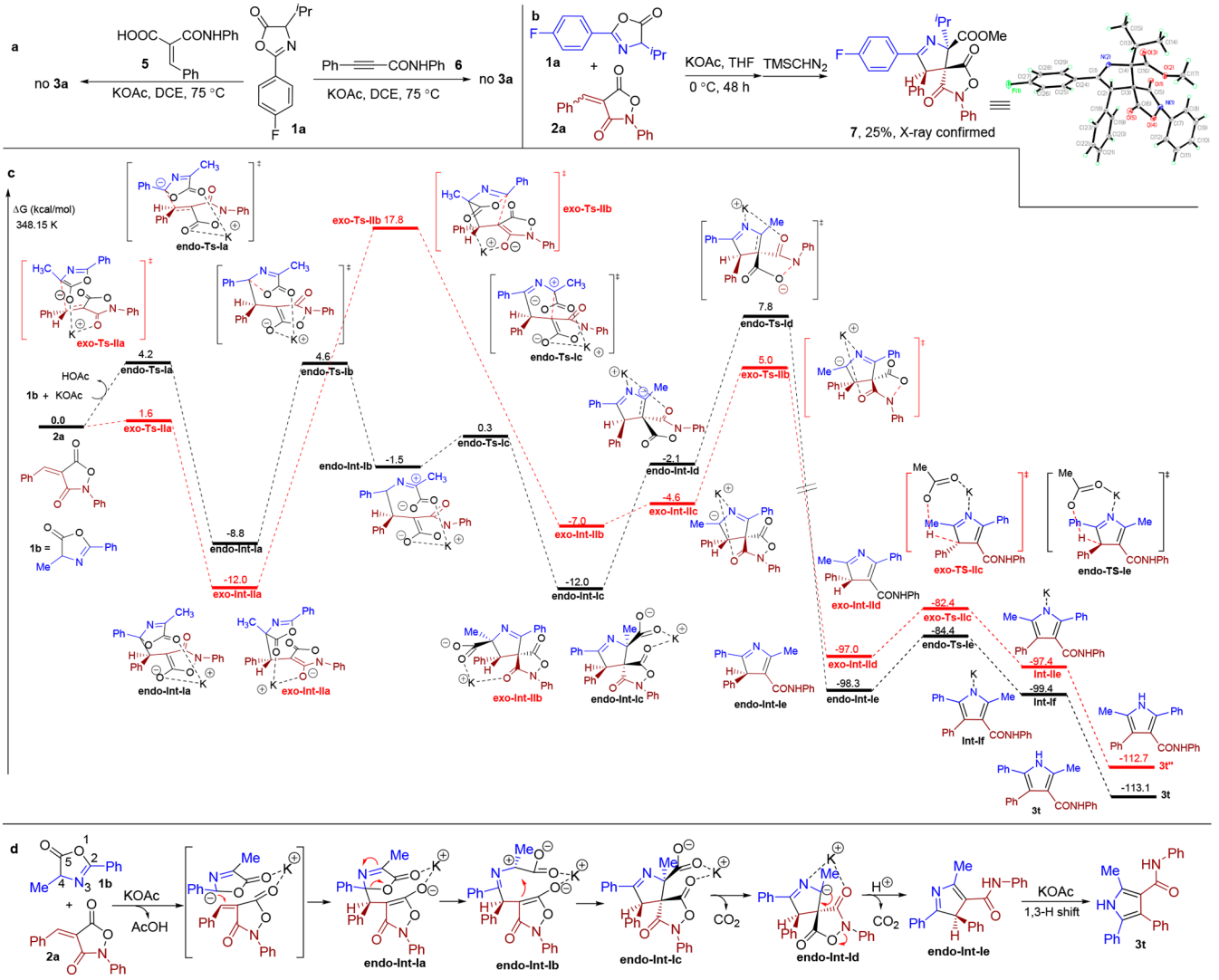
Scheme 5. Depictions of (a, b) Mechanistic Studies, (c) DFT Calculations, and (d) Proposed Mechanism



in Scheme 5d. In the presence of a basic potassium salt, oxazolone **1b** is first deprotonated and 1,4-nucleophilic attacks at the C2 position of isoxazolidinedione **2a** in an *endo* manner. The key spirocyclic intermediate **endo-Int-Ic** would be formed after stepwise events consisting of ring opening and intramolecular addition. Subsequently, two rounds of decarboxylation proceed rapidly to produce a pyrrole precursor **endo-Int-Ie**. Finally, the desired pyrrole product **3t** will be generated after fast occurring of KOAc-assisted 1,3-hydrogen shift (isomerization).

In summary, a novel KOAc-catalyzed double decarboxylative transannulation reaction by taking advantage of traceless activating and directing strategy has been devised for the first time. This skeletal remodeling transformation provides an effective method for the expedient preparation of tetrasubstituted 3-carbamoyl-4-aryl NH-pyrroles with a wide substrate scope and excellent level of regioselectivity. The mild, robust, environmentally friendly, and operationally simple features render this strategy very practical for the divergent synthesis of versatile pyrrole pharmacores, as demonstrated by the preparation of various Atorvastatin analogues in a chemodivergent and regiodivergent manner. Further studies on the application of this tactic to other substrate classes are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03621.

Experimental procedures, characterization data, NMR spectra, and computational details (PDF)

Accession Codes

CCDC 1938705−1938707 and 1947323 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) (a) van Leeuwen, P. W. N. M. *Homogeneous Catalysis: Understanding the Art*; Kluwer Academic Publishers: Dordrecht, The Netherlands, 2004. (b) Knochel, P.; Molander, G. A. *Comprehensive Organic Synthesis*, 2nd Edition; Elsevier: Amsterdam, 2014.

(2) (a) Sun, C.; Shi, Z.-J. Transition-Metal-Free Coupling Reactions. *Chem. Rev.* **2014**, *114*, 9219−9280. (b) Chirik, P.; Morris, R. Getting Down to Earth: The Renaissance of Catalysis with Abundant Metals. *Acc. Chem. Res.* **2015**, *48*, 2495. (c) White, M. C. Base-Metal Catalysis: Embrace the Wild Side. *Adv. Synth. Catal.* **2016**, *358*, 2364−2365. (d) Ilies, L.; Thomas, S. P.; Tonks, I. A. Earth-Abundant Metals in Catalysis. *Asian J. Org. Chem.* **2020**, *9*, 324−325.

(3) Haynes, W. M. *CRC Handbook of Chemistry and Physics*, 97th Edition; CRC Press, 2016; pp 14−17.

(4) Toutov, A. A.; Liu, W.-B.; Betz, K. N.; Fedorov, A.; Stoltz, B. M.; Grubbs, R. H. Silylation of C−H bonds in aromatic heterocycles by an Earth-abundant metal catalyst. *Nature* **2015**, *518*, 80−84.

(5) Sun, C.-L.; Li, H.; Yu, D.-G.; Yu, M.; Zhou, X.; Lu, X.-Y.; Huang, K.; Zheng, S.-F.; Li, B.-J.; Shi, Z.-J. An efficient organocatalytic method for constructing biaryls through aromatic C−H activation. *Nat. Chem.* **2010**, *2*, 1044−1049.

(6) Shi, Q.; Zhang, S.; Zhang, J.; Oswald, V. F.; Amassian, A.; Marder, S. R.; Blakey, S. B. KO^{t}Bu-Initiated Aryl C−H Iodination: A Powerful Tool for the Synthesis of High Electron Affinity Compounds. *J. Am. Chem. Soc.* **2016**, *138*, 3946−3949.

(7) Kumar, A.; Janes, T.; Chakraborty, S.; Daw, P.; von Wolff, N.; Carmieli, R.; Diskin-Posner, Y.; Milstein, D. C−C Bond Formation of Benzyl Alcohols and Alkynes Using a Catalytic Amount of KO^{t}Bu: Unusual Regioselectivity through a Radical Mechanism. *Angew. Chem., Int. Ed.* **2019**, *58*, 3373−3377.

(8) (a) Toutov, A. A.; Betz, K. N.; Schuman, D. P.; Liu, W.-B.; Fedorov, A.; Stoltz, B. M.; Grubbs, R. H. Alkali Metal-Hydroxide-Catalyzed C(sp)−H Bond silylation. *J. Am. Chem. Soc.* **2017**, *139*, 1668−1674. (b) Wang, X.; Zhu, M.-H.; Schuman, D. P.; Zhong, D.; Wang, W.-Y.; Wu, L.-Y.; Liu, W.; Stoltz, B. M.; Liu, W.-B. General and Practical Potassium Methoxide/Disilane-Mediated Dehalogenative Deuteration of (Hetero)Arylhalides. *J. Am. Chem. Soc.* **2018**, *140*, 10970−10974. (c) Barham, J. P.; Coulthard, G.; Emery, K. J.; Doni, E.; Cumine, F.; Nocera, G.; John, M. P.; Berlouis, L. E. A.; McGuire, T.; Tuttle, T.; Murphy, J. A. KO^{t}Bu: A Privileged Reagent for Electron Transfer Reactions? *J. Am. Chem. Soc.* **2016**, *138*, 7402−7410. (d) Xu, Y.; Zhang, S.; Li, L.; Wang, Y.; Zha, Z.; Wang, Z. L-Phenylalanine potassium catalyzed asymmetric formal [3 + 3] annulation of 2-enoyl-pyridine *N*-oxides with acetone. *Org. Chem. Front.* **2018**, *5*, 376−379.

(9) (a) Hartner, F., Jr.; Katritzky, A.; Rees, C.; Scriven, E. *Comprehensive Heterocyclic Chemistry II*, Vol. *2*; Pergamon Press: Oxford, U.K., 1996. (b) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. Lamellarins and Related Pyrrole-Derived Alkaloids from Marine Organisms. *Chem. Rev.* **2008**, *108*, 264−287. (c) Proto, M. C.; Fiore, D.; Forte, G.; Cuozzo, P.; Ramunno, A.; Fattorusso, C.; Gazzerro, P.; Pascale, M.; Franceschelli, S. Tetra-substituted pyrrole derivatives act as potent activators of p53 in melanoma cells. *Invest. New Drugs* **2020**, *38*, 634−649.

(10) Roth, B. D. The discovery and development of atorvastatin, a potent novel hypolipidemic agent. *Prog. Med. Chem.* **2002**, *40*, 1−22.

(11) Le Tourneau, C.; Raymond, E.; Faivre, S. Sunitinib: a novel tyrosine kinase inhibitor. A brief review of its therapeutic potential in the treatment of renal carcinoma and gastrointestinal stromal tumors (GIST). *Ther. Clin. Risk Manag.* **2007**, *3*, 341−348.

(12) Cicero, A. FG; Laghi, L. Activity and potential role of licofelone in the management of osteoarthritis. *Clin. Interv. Aging* **2007**, *2*, 73−79.

(13) Zheng, W.; Rampe, D.; Triggle, D. J. Pharmacological, radioligand binding, and electrophysiological characteristics of FPL

64176, a novel nondihydropyridine Ca^{2+} channel activator, in cardiac and vascular preparations. *J. Mol. Pharmacol.* **1991**, *40*, 734−741.
(14) Pimprale, S. S.; Besco, C. L.; Bryson, E. K.; Brown, T. M. Increased Susceptibility of Pyrethroid-Resistant Tobacco Budworm (Lepidoptera: Noctuidae) to Chlorfenapyr. *J. Econ. Entomol.* **1997**, *90*, 49−54.
(15) Rudi, A.; Goldberg, I.; Stein, Z.; Frolow, F.; Benayahu, Y.; Schleyer, M.; Kashman, Y. Polycitone A and Polycitrins A and B: New Alkaloids from the Marine Ascidian Polycitor sp. *J. Org. Chem.* **1994**, *59*, 999−1003.
(16) (a) Cox, M.; Lehninger, A. L.; Nelson, D. R. *Lehninger Principles of Biochemistry*; Worth Publishers: New York, 2000. (b) de Montellano, P. R. O. Hemes in Biology. In *Wiley Encyclopedia of Chemical Biology*; John Wiley & Sons, 2008, DOI: 10.1002/9780470048672.wecb221. (c) Ulrich, G.; Ziessel, R.; Harriman, A. The Chemistry of Fluorescent Bodipy Dyes: Versatility Unsurpassed. *Angew. Chem., Int. Ed.* **2008**, *47*, 1184−1201. (d) Hagfeldt, A.; Boschloo, G.; Sun, L.; Kloo, L.; Pettersson, H. Dye-Sensitized Solar Cells. *Chem. Rev.* **2010**, *110*, 6595−6663.
(17) (a) Patil, N. T.; Yamamoto, Y. Coinage Metal-Assisted Synthesis of Heterocycles. *Chem. Rev.* **2008**, *108*, 3395−3442. (b) Estévez, V.; Villacampa, M.; Menéndez, J. C. Recent advances in the synthesis of pyrroles by multicomponent reactions. *Chem. Soc. Rev.* **2014**, *43*, 4633−4657. (c) Bhardwaj, V.; Gumber, D.; Abbot, V.; Dhiman, S.; Sharma, P. Pyrrole: a resourceful small molecule in key medicinal hetero-aromatics. *RSC Adv.* **2015**, *5*, 15233−15266. (d) Zou, Y.-Q.; Lu, L.-Q.; Fu, L.; Chang, N.-J.; Rong, J.; Chen, J.-R.; Xiao, W.-J. Visible-Light-Induced Oxidation/[3 + 2] Cycloaddition/Oxidative Aromatization Sequence: A Photocatalytic Strategy To Construct Pyrrolo[2,1-a]isoquinolines. *Angew. Chem., Int. Ed.* **2011**, *50*, 7171−7175. (e) Humenny, W. J.; Kyriacou, P.; Sapeta, K.; Karadeolian, A.; Kerr, M. A. Multicomponent Synthesis of Pyrroles from Cyclopropanes: A One-Pot Palladium(0)-Catalyzed Dehydrocarbonylation/Dehydration. *Angew. Chem., Int. Ed.* **2012**, *51*, 11088−11091. (f) Geng, W.; Zhang, W.-X.; Hao, W.; Xi, Z. Cyclopentadiene−Phosphine/Palladium-Catalyzed Cleavage of C−N Bonds in Secondary Amines: Synthesis of Pyrrole and Indole Derivatives from Secondary Amines and Alkenyl or Aryl Dibromides. *J. Am. Chem. Soc.* **2012**, *134*, 20230−20233. (g) Parr, B. T.; Green, S. A.; Davies, H. M. L. Rhodium-Catalyzed Conversion of Furans to Highly Functionalized Pyrroles. *J. Am. Chem. Soc.* **2013**, *135*, 4716−4718. (h) Xuan, J.; Xia, X.-D.; Zeng, T.-T.; Feng, Z.-J.; Chen, J.-R.; Lu, L.-Q.; Xiao, W.-J. Visible-Light-Induced Formal [3 + 2] Cycloaddition for Pyrrole Synthesis under Metal-Free Conditions. *Angew. Chem., Int. Ed.* **2014**, *53*, 5653−5656. (i) Wang, Y.; Lei, X.; Tang, Y. Rh(II)-catalyzed cycloadditions of 1-tosyl 1,2,3-triazoles with 2*H*-azirines: switchable reactivity of Rh-azavinylcarbene as [2C]- or aza-[3C]-synthon. *Chem. Commun.* **2015**, *51*, 4507−4510. (j) Lei, X.; Li, L.; He, Y.-P.; Tang, Y. Rhodium(II)-Catalyzed Formal [3 + 2] Cycloaddition of *N*-Sulfonyl-1,2,3-triazoles with Isoxazoles: Entry to Polysubstituted 3-Aminopyrroles. *Org. Lett.* **2015**, *17*, 5224−5227. (k) Lin, Z.-Q.; Li, C.-D.; Zhou, Z.-C.; Xue, S.; Gao, J.-R.; Ye, Q.; Li, Y.-J. Copper(II)-Promoted Oxidation/[3 + 2]Cycloaddition/ Aromatization Cascade: Efficient Synthesis of Tetrasubstituted NH-Pyrrole from Chalcones and Iminodiacetates. *Synlett* **2019**, *30*, 1442−1446. (l) 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. (m) 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.
(18) (a) Chen, Z.; Zheng, Y.; Ma, J.-A. Use of a Traceless Activating and Directing Group for the Construction of Trifluoromethylpyrazoles: One-Pot Transformation of Nitroolefins and Trifluorodiazoethane. *Angew. Chem., Int. Ed.* **2017**, *56*, 4569−4574. (b) Zeng, J.-L.; Chen, Z.; Zhang, F.-G.; Ma, J.-A. Direct Regioselective [3 + 2] Cycloaddition Reactions of Masked Difluorodiazoethane with Electron-Deficient Alkynes and Alkenes: Synthesis of Difluoromethyl-Substituted Pyrazoles. *Org. Lett.* **2018**, *20*, 4562−4565. (c) Chen, Z.; Ren, N.; Ma, X.; Nie, J.; Zhang, F.-G.; Ma, J.-A. Silver-Catalyzed [3 + 3] Dipolar Cycloaddition of Trifluorodiazoethane and Glycine Imines: Access to Highly Functionalized Trifluoromethyl-Substituted Triazines and Pyridines. *ACS Catal.* **2019**, *9*, 4600−4608.
(19) Two patents related to this work have been submitted to the National Intellectual Property Administration of China, under the process numbers CN110878059 and CN111362855.
(20) (a) Feng, X. X.; Tong, B.; Shen, J.-B.; Shi, J.-B.; Han, T.-Y.; Chen, L.; Zhi, J.-G.; Lu, P.; Ma, Y.-G.; Dong, Y.-P. Aggregation-Induced Emission Enhancement of Aryl-Substituted Pyrrole Derivatives. *J. Phys. Chem. B* **2010**, *114*, 16731−16736. (b) Zhang, C.; Zhu, X. Thieno[3,4-b]thiophene-Based Novel Small-Molecule Optoelectronic Materials. *Acc. Chem. Res.* **2017**, *50*, 1342−1350.
(21) Kim, M.-S.; Yoo, M.-H.; Rhee, J.-K.; Kim, Y.-J.; Park, S.-J.; Choi, J.-H.; Sung, S.-Y.; Lim, H.-G.; Cha, D.-W. *Synthetic Intermediates, Process for Preparing Pyrrolyl-heptanoic acid derivatives Therefrom*. International Patent No. WO 2009084827, 2009.
(22) Roth, B. D.; Blankley, C. J.; Chucholowski, A. W.; Ferguson, E.; Hoefle, M. L.; Ortwine, D. F.; Newton, R. S.; Sekerke, C. S.; Sliskovic, D. R.; Wilson, M. W. Inhibitors of Cholesterol Biosynthesis. 3. Tetrahydro-4-hydroxy-6-[2-(1*H*-pyrrol-l-yl)ethyl]-2*H*-pyran-2-one Inhibitors of HMG-CoA Reductase. 2. Effects of Introducing Substituents at Positions Three and Four of the Pyrrole Nucleus. *J. Med. Chem.* **1991**, *34*, 357−366.

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