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Brønsted Acid-Catalyzed Formal [2 + 2 + 1] Annulation for the Modular Synthesis of Tetrahydroindoles and Tetrahydrocyclopenta[*b*]pyrroles

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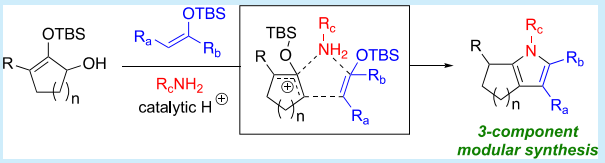
Supporting Information

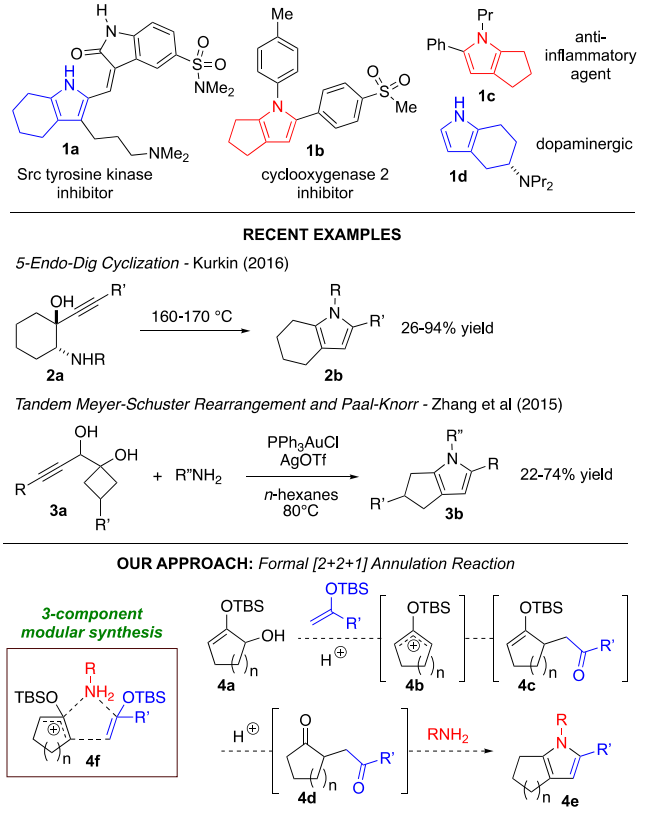
ABSTRACT: An expedient synthesis of tetrahydroindoles and tetrahydrocyclopenta[*b*]pyrroles, highlighted by Brønsted acid catalyzed formal [2 + 2 + 1] annulation reaction, is reported. Using three readily accessible reaction components, i.e., an electrophilic species in silyloxyallyl cations and two distinct nucleophiles in silylenol ethers and amines, our chemistry enables the assembly and functionalization of these biologically important *N*-heterocycles in a highly modular manner.



Tetrahydroindoles and tetrahydrocyclopenta[*b*]pyrroles are a class of nitrogen-containing heterocycles of biological importance.[1] Exemplified in compounds **1a** to **1c**, these molecular structures are pharmacophores in molecules that serve as an anti-inflammatory agent,[1a] or inhibitors for cyclooxygenase 2,[1b] and Src tyrosine kinase.[1c] It has also been reported that tetrahydroindole **1d** exhibits selective dopaminergic activities.[1d] Natural products, such as microindolinone A and (+)-roseophilin,[2] also possess these ring motifs as a key feature to their architectures. Due to their biological contexts, the development of synthetic reactions that readily assemble tetrahydroindoles and tetrahydrocyclopenta[*b*]pyrroles remains an important synthetic endeavor.[3] Scheme 1 illustrates recent advancements. Kurkin reported a solvent-free approach to tetrahydroindole core **2b**, which was achieved via heat-induced 5-*endo-dig* cyclization of amino propargylic alcohols **2a**.[3c,d] Unlike tetrahydroindoles, literature precedents on the construction of tetrahydrocyclopenta[*b*]pyrroles are scarce.[4] One of which was reported by Zhang who demonstrated that exposure of alkyne diols **3a** to catalytic PPh_3AuCl and AgOTf in the presence of amines produced tetrahydrocyclopenta[*b*]-pyrrole **3b**, which occurred via Meyer−Schuster rearrangement and Paal−Knorr cyclization cascade.[4a]

Combined with the use of expensive organometallic catalysts to induce ring formation, many of the elegant chemistries to construct tetrahydroindoles and tetrahydrocyclopenta[*b*]-pyrroles rely on linear preconstruction of the substrates prior to cyclization. These strategies are at a disadvantage in terms of enabling the introduction of a vast array of functionalities to these rings in an expedient manner, a practice that is essential in drug discovery.[5] Herein we describe our approach toward broadly substituted tetrahydroindoles and tetrahydro-cyclopenta[*b*]pyrroles, which will be enabled by two distinct nucleophiles in silylenol ethers and primary amines, and an electrophile in silyloxyallyl cations that will be generated *in situ* upon ionization of α-hydroxy silylenol ether **4a**. Catalyzed by Brønsted acid,[6,7] these three simple modular components

Scheme 1. Synthetic Methods to Access Tetrahydroindoles and Tetrahydrocyclopenta[*b*]pyrroles



should readily undergo a formal [2 + 2 + 1] annulation reaction as represented in framework **4f**. Our rationale is as

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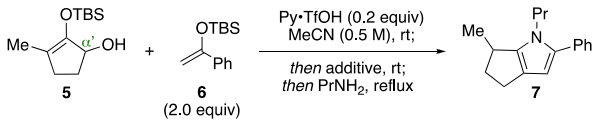
follows. The regioselective interception of silyloxyallyl cations **4b** with silylenol ether should create a new C−C connectivity in the resulting γ-keto silylenol ether **4c**.[7] The ensuing protodesilylation under the Brønsted acidic conditions will produce 1,4-diketone **4d**. In the presence of primary amine, the Paal-Knorr condensation should occur,[8] thus completing our synthesis of tetrahydroindole and tetrahydrocyclopenta[*b*]-pyrrole motifs **4e**.

Our proof-of-concept and reaction optimization is summarized in Table 1,[9] in which α′-hydroxy silylenol ether **5**, acetophenone-derived silylenol ether **6**, and propylamine were employed as model substrates. As shown in entry 1, we began by subjecting compounds **5** and **6** to catalytic pyridinium triflate in acetonitrile at room temperature to allow formation of the key monosilylated 1,4-diketone construct in a regioselective manner.[7a] Excess propylamine was then added to the mixture after complete consumption of α′-hydroxy silylenol ether **5** and the ensuing protodesilylation as easily monitored by TLC, and the reaction was then warmed to reflux. Interestingly, this pilot experiment indeed led to the formation tetrahydrocyclopenta-[*b*]pyrrole **7**, which was isolated in 77% yield after 7 days of reaction time. We noted while the coupling of α′-hydroxy silylenol ether **5** with silylenol ether **6** concluded in just approximately 1 h, the rate-determining steps in these initial conditions appeared to be controlled by protodesilylation of the forming γ-keto silylenol ether.

Table 1. Reaction Optimization



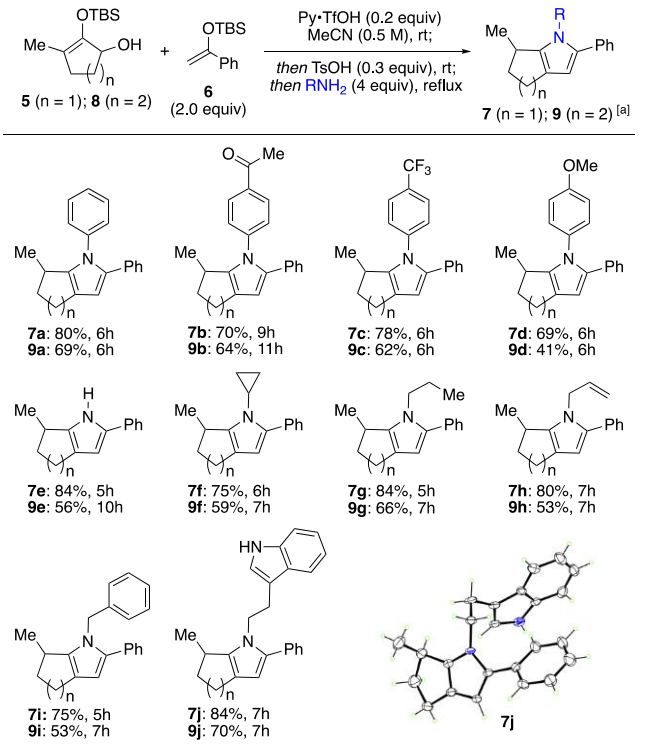
entry	additive	additive equiv.	$PrNH_2$ equiv.	total reaction time (h)	yield[a] (%)
1	-	-	4.0	168	77
2	PPTS	0.5	4.0	96	74
3	TfOH	0.5	4.0	4	62
4	CSA	0.5	4.0	8	82
5	TsOH	0.5	4.0	6	83
6	**TsOH**	**0.3**	**4.0**	**5**	**83**
7	TsOH	0.2	4.0	8	77
8	TsOH	0.3	2.0	7	75
9	TsOH	0.3	4.0	192	56[b]

[a]Isolated yield after column chromatography. [b]Reaction was performed at room temperature.

Following this initial result, we focused our efforts to improve the protodesilylation sequence with a notion that the efficiency of this step could be affected by an introduction of an additive, such as a secondary Brønsted acid catalyst. As shown in entries 2−5, our hypothesis was tested through the screening of pyridinium tosylate, triflic acid, camphorsulfonic acid, and tosic acid monohydrate. These additives were added in the amount of 0.5 mol equiv after completion of the preceding reaction between α′-hydroxy silylenol ether **5** and silylenol ether **6**, but before the addition of propylamine. Indeed, the addition of stronger Brønsted acids substantially enhanced the rate of protodesilylation. To this end, we ultimately chose tosic acid. Entries 5−8 indicate that the molar amount of tosic acid or propylamine could be further reduced without notably affecting the robustness of the reaction. Nonetheless, the efficiency of Paal-Knorr condensation diminished dramatically without heat (entry 9). Overall, our optimized conditions are as follows: ensuing the coupling between α′-hydroxy silylenol ether **5** and 2.0 equiv of silylenol ether **6** promoted by 0.2 equiv of pyridinium triflate in acetonitrile at room temperature, 0.3 equiv of tosic acid monohydrate was introduced to induce protodesilylation. After the addition of 4.0 equiv of propylamine, the mixture was warmed to reflux, furnishing tetrahydrocyclopenta[*b*]pyrrole **7** in 83% yields in just 5 h of total reaction time.

To identify the scope of our method, we began by screening the applicability of various primary amines (Scheme 2). In these studies, both 5- and 6-membered α-hydroxy silylenol ethers **5** and **8** were employed to furnish a diverse library of *N*-substituted tetrahydrocyclopenta[*b*]pyrrole and tetrahydroindole **7** and **9**, respectively. Commencing with aniline and its derivatives, i.e., 4-trifluoromethylaniline, 4-aminoacetophenone, and 4-methoxy-aniline, our reaction successfully produced the corresponding adducts **7a**−**7d** and **9a**−**9d** in good yields. Interestingly, the use of ammonia as the Paal-Knorr reactant furnished unprotected *N*-heterocyclic core **7e** and **9e** in 84% and 56% yields, respectively. Cyclopropylamine, propylamine, allylamine, and benzylamine were tolerated by our reaction conditions. These aliphatic amines furnished the corresponding tetrahydrocyclopenta[*b*]pyrrole **7f**−**7i** and tetrahydroindole **9f**−**9i** again in excellent yields within several hours of reaction time. We also subjected neurotransmitter tryptamine, which produced tethered heterocyclic motifs **7j** and **9j** in 84% and 70% yields, respectively. Compounds **7j** and **9a** existed in the crystalline form, allowing us to assign their structure by X-ray diffraction.[10] Interestingly, these experiments revealed formation of 6-membered tetrahydroindole **9**

Scheme 2. Scope of Amines



[a]Isolated yield after column chromatography.

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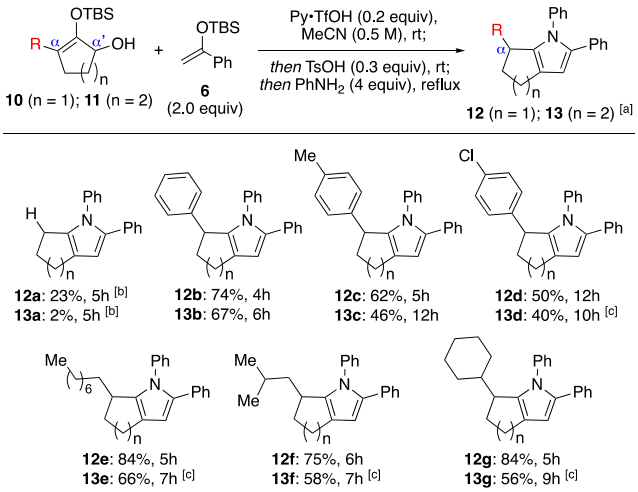
was generally lower yielding than that of its 5-membered counterpart **7**. This phenomenon is most likely stemmed from challenges associated with the generation of 6-membered silyloxyallyl cations from the corresponding α'-hydroxy silylenol ether **5**.[11]

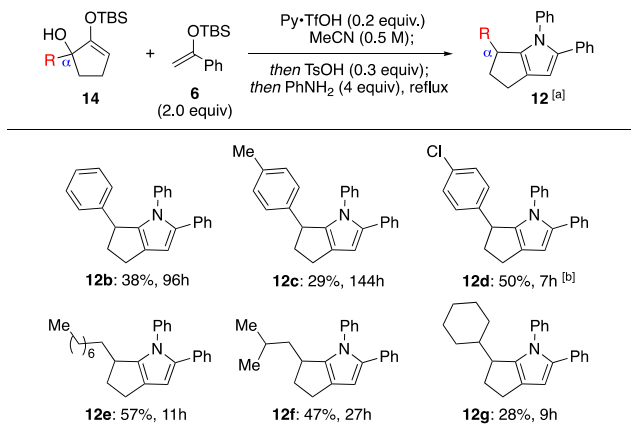
Our investigation continued with substituent effects at the α-carbon. In this study, we employed a series of secondary α'-hydroxy silylenol ethers **10** and **11** in the presence of silylenol ether **6** and aniline as coupling partners. Schemes 3 and 4 depict our results, starting with the use of unsubstituted α'-hydroxy silylenol ethers, which led to products **12a** and **13a**, however in poor yields due to decomposition of materials under the reaction conditions. Nonetheless, our method was tolerated by both aromatic and aliphatic substituents at the α-carbon. For instance, arene-bearing substrates, such as phenyl, toluoyl, and *p*-chlorophenyl, readily afforded tetrahydrocyclopenta[*b*]pyrrole **12b**–**12d** and tetrahydroindole **13b**–**13d** in high yields. A slower rate of reaction and diminishing yield of the products involving chlorine-containing starting materials was noted. With respect to the aliphatic variants, we explored linear *n*-octyl chain as well as branched isobutyl and cyclohexyl groups. Interestingly, steric effects did not play significant role, as the resulting 5-membered products **12e**–**12g** and 6-membered products **13e** and **13g** were all isolated in high yields. We also observed that several of the 6-membered substrates required a higher loading of silylenol ether **6** to improve the rate of the initial coupling reaction. Due to their crystalline form, we were able to confirm the structures of **13b** and **13g** by X-ray diffraction.[10]

Scheme 3. Substituent Effects



[a]Isolated yield after column chromatography. [b]The reaction was performed in 0.2 M concentration using 4.0 equiv of silylenol ether **6**. [c]3.0 equiv of silylenol ether **6** was employed.

Scheme 4. Alternate Substrates[a]



[a][a]Isolated yield after column chromatography. [b]3.0 equiv of silylenol ether **7** was employed.

Our previous studies revealed that unsymmetrical silyloxyallyl cations could be effectively generated from tertiary α-hydroxy silylenol ethers.[6] To examine the utility of this alternate substrate motif in this chemistry, we subjected a series of 5-membered starting materials **14** that were elaborated with identical aromatic and aliphatic substituents at the α-carbon to those of substrates **10**. Indeed, exposure of these compounds to our method furnished target products **12b**–**12g**. Nonetheless, a substantial attrition in the product yields was observed, as these substrates could not be fully consumed despite the prolonged reaction time. We suspected that the underlying cause for this phenomenon lay in the steric barrier imposed by the tertiary alcohols, therefore slowing the rate of ionization and ultimately prompting competitive quenching of the catalyst by either silylenol ether **6** or α-hydroxy silylenol ethers **14** via protodesilylation.

Using both 5-membered and 6-membered substrates **5** and **8** and propylamine as the coupling partners, we then varied silylenol ethers **15** to demonstrate our ability to expediently diversify the C2 and C3 positions of tetrahydrocyclopenta[*b*]-pyrrole **16** and tetrahydroindole **17** (Table 2). Interestingly, we identified in some 6-membered systems that protodesilylation of the resulting γ-keto silylenol ether constructs unexpectedly led to concomitant intramolecular cyclization, prior to addition of propylamine, therefore affording tetrahydrobenzofuran byproducts. To circumvent this undesired furan annulation, we produced an alternate set of protodesilylation conditions to unmask the 1,4-diketone motif using CsF at reflux (Conditions B).[9] This protocol was followed by addition of TsOH and propylamine to affect the Paal-Knorr condensation.

With the two complementary conditions in hand, we subjected acetophenone-derived silylenol ethers bearing electronically opposing trifluoromethyl and methoxy groups (entries 1 and 2), revealing that the electron-deficient group appeared to be less robust. Our method allows for simultaneous incorporation of functional groups at the C2 and C3 positions of the forming heterocycles. For instance, α-tetralone and cyclohexanone derived silylenolates were found to be compatible to furnish their respective polycyclic adducts **16c** and **16d** as well as **17c** and **17d** in good yields. As shown in entry 5, we employed a highly substituted silylenol ether that was prepared from 3-pentanone. This nucleophile selectively introduced C2-ethyl and C3-methyl substituents in products **16e** and **17e** with 50% and 54% isolated yields, respectively. A similar observation was noted when 2-phenylacetophenone derived silylenol ether nucleophile was applied to our reaction (entry 6). In this case, the resulting tetrahydrocyclopenta[*b*]-pyrrole **16f** and tetrahydroindole **17f**, both of which were decorated with two phenyl groups at the pyrrole moiety, were isolated in good yields. Finally, we attempted to elaborate exclusively on the C3 position using phenylacetaldehyde derived nucleophile (entry 7). While the resulting annulation product **16g** was accessible from 5-membered substrate **5** in

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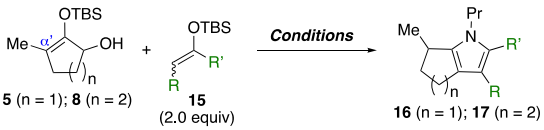
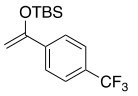
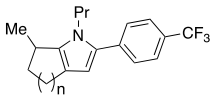
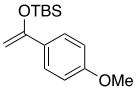
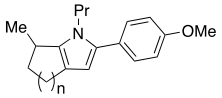
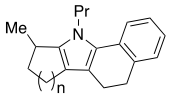
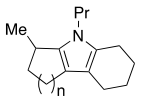
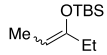
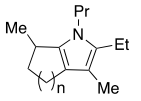
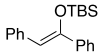
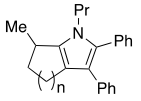
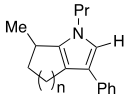
Table 2. Scope of Silylenol Ethers



Conditions A: Py•TfOH (0.2 equiv), MeCN (0.5 M), rt; *then* TsOH (0.3 equiv), rt; *then* propylamine (4.0 equiv), reflux

Conditions B: Py•TfOH (0.2 equiv), MeCN (0.5M), rt; *then* CsF (2.0 equiv), reflux; *then* TsOH (1.0 equiv), propylamine (4.0 equiv), reflux

entry	nucleophile	product	cond.	time (h)	yield [a]
1			A B	27 11	**16a**: 52% **17a**: 34%
2			A A	5 5	**16b**: 66% **17b**: 55%
3			A A	31 30	**16c**: 50% **17c**: 50%
4			A B	6 8	**16d**: 64% **17d**: 51%
5			A B	5 9	**16e**: 50% **17e**: 54%
6			A B	19 100 [b]	**16f**: 62% **17f**: 46%
7			A A / B	6 -	**16g**: 36% **17g**: decomp

[a]Isolated yield after column chromatography. [b]Substrate **8** was not fully consumed despite the prolonged reaction time.

36% yield, an application to starting material **8** was not fruitful, as such a reaction under either condition only led to decomposition of materials.

In summary, we have developed a robust one-pot chemistry to construct highly substituted tetrahydroindoles and tetrahydrocyclopenta[*b*]pyrroles under mild catalytic conditions. Highlighted by a formal [2 + 2 + 1] annulation reaction that involves three reaction partners in silyloxyallyl cations, silylenolates, and primary amines, our method successfully produced these biologically significant *N*-heterocycles in good yields. Applications of our strategy to access structurally related heterocycles and complex molecules are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.9b01032.

Experimental procedures and spectral data of new compounds (PDF)

Accession Codes

CCDC 1894940−1894943 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) Xu, X. T.; Mou, X. Q.; Xi, Q. M.; Liu, W. T.; Liu, W. F.; Sheng, Z. J.; Zheng, X.; Zhang, K.; Du, Z. Y.; Zhao, S. Q.; Wang, S. H. Anti-inflammatory Activity Effect of 2-Substituted-1,4,5,6-tetrahydrocyclopenta[b]pyrrole on TPA-induced Skin Inflammation in Mice. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5334. (b) Zhong, B.; Li, M. *Preparation of Pyrrole Derivatives as Cyclooxygenase 2 Inhibitors*. Chinese Patent CN1955163A. (c) Guan, H. P.; Laird, A. D.; Blake, R. A.; Tang, C.; Liang, C. Design and Synthesis of Aminopropyl Tetrahydroindole-Based Indolin-2-ones as Selective and Potent Inhibitors of Src and Yes Tyrosine Kinase. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 187. (d) Bergauer, M.; Hubner, H.; Gmeiner, P. Practical Ex-chiral-pool Methodology for the Synthesis of Dopaminergic Tetrahydroindoles. *Tetrahedron* **2004**, *60*, 1197. (e) Fatahala, S. S.; Shalaby, E. A.; Kassab, S. E.; Mohamed, M. S. A Promising Anti-cancer and Anti-oxidant Agents Based on the Pyrrole and Fused Pyrrole: Synthesis, Docking Studies and Biological Evaluation. *Anti-Cancer Agents Med. Chem.* **2015**, *15*, 517. (f) Henne, P.; Zeeck, A.; Grabley, S.; Thiericke, R. Secondary Metabolites by Chemical Screening. 35. 6,7-Dihydroxy-4,5,6,7-tetrahydroindole-4-one, a New Type of Indole-derivative from *Nocardia sp*. *Nat. Prod. Lett.* **1997**, *10*, 43. (g) Sun, L.; Tran, N.; Liang, C. X.; Hubbard, S.; Tang, F.; Lipson, K.; Schreck, R.; Zhou, Y.; McMahon, G.; Tang, C. Identification of Substituted 3-(4,5,6,7-Tetrahydro-1H-indol-2-yl)methylene-1,3-dihydroindol-2-ones as Growth Factor Receptor Inhibitors for VEGF-R2 (Flk-1/KDR), FGF-R1, and PDGF-R betav Tyrosine Kinases. *J. Med. Chem.* **2000**, *43*, 2655. (h) Tarzia, G.; Duranti, A.; Tontini, A.; Spadoni, G.; Mor, M.; Rivara, S.; Plazzi, P. V.; Kathuria, S.; Piomelli, D. Synthesis and Structure-Activity Relationships of a Series of Pyrrole Cannabinoid Receptor Agonists. *Bioorg. Med. Chem.* **2003**, *11*, 3965.

(2) (a) Niu, S. W.; Zhou, T. T.; Xie, C. L.; Zhang, G. Y.; Yang, X. W. Microindolinone A, a Novel 4,5,6,7-Tetrahydroindole, From the Deep-sea-derived Actinomycete Microbacterium sp MCCC 1A11207.

DOI: 10.1021/acs.orglett.9b01032
Org. Lett. XXXX, XXX, XXX−XXX

Mar. Drugs **2017**, *15*, 230. (b) Furstner, A. Chemistry and Biology of Roseophilin and the Prodigiosin Alkaloids: A Survey of the Last 2500 Years. *Angew. Chem., Int. Ed.* **2003**, *42*, 3582. (c) Hayakawa, Y.; Kawakami, K.; Seto, H.; Furihata, K. Structure of a New Antibiotic, Roseophilin. *Tetrahedron Lett.* **1992**, *33*, 2701.

(3) (a) Brayton, D. F.; Beaumont, P. R.; Fukushima, E. Y.; Sartain, H. T.; Morales-Morales, D.; Jensen, C. M. Synthesis, Characterization, and Dehydrogenation Activity of an Iridium Arsenic Based Pincer Catalyst. *Organometallics* **2014**, *33*, 5198. (b) Brayton, D. F.; Jensen, C. M. Solvent Free Selective Dehydrogenation of Indolic and Carbazolic Molecules with an Iridium Pincer Catalyst. *Chem. Commun.* **2014**, *50*, 5987. (c) Andreev, I. A.; Ratmanova, N. K.; Novoselov, A. M.; Belov, D. S.; Seregina, I. F.; Kurkin, A. V. Synthesis of 4,5,6,7-Tetrahydro-1H-indole Derivatives Through Successive Sonogashira Coupling/Pd-Mediated 5-endo-dig Cyclization. *Chem. - Eur. J.* **2016**, *22*, 7262. (d) Andreev, I. A.; Belov, D. S.; Kurkin, A. V.; Yurovskaya, M. A. Oxidative Dearomatization of 4,5,6,7-Tetrahydro-1H-indoles Obtained by Metal- and Solvent-Free Thermal 5-endo-dig Cyclization: The Route to Erythrina and Lycorine Alkaloids. *Eur. J. Org. Chem.* **2013**, *2013*, 649. (e) Xue, S. W.; Li, Y.; Wang, L. H.; Liu, J. M.; Qing, X. S.; Wang, C. D. Four-Component Reaction of Substituted Nitrostyrenes, Cyclohexanones, Activated Methylene Compounds, and Ammonium Acetate: Efficient Strategy for Construction of Tetrahydroindole Skeletons. *Synlett* **2016**, *27*, 1083. (f) Mamedov, V. A.; Hafizova, E. A.; Zamaletdinova, A. I.; Rizvanov, I. K.; Mirgorodskaya, A. B.; Zakharova, L. Y.; Latypov, S. K.; Sinyashin, O. G. Sequential Substitution/ring cleavage/addition Reaction of 1-(Cyclohex-1-enyl)-piperidine and -Pyrrolidine with Chloropyruvates for the Efficient Synthesis of Substituted 4,5,6,7-Tetrahydro-1H-indole Derivatives. *Tetrahedron* **2015**, *71*, 9143. (g) To, Q. H.; Lee, Y. R.; Kim, S. H. One-step Synthesis of Tetrahydroindoles by Ceric(IV) Ammonium Nitrate-Promoted Oxidative Cycloaddition of Enaminones and Vinyl Ethers. *Tetrahedron* **2014**, *70*, 8108. (h) Shi, Q. Q.; Fu, L. P.; Shi, Y.; Ding, H. Q.; Luo, J. H.; Jiang, B.; Tu, S. J. Three-component Synthesis of Poly-Substituted Tetrahydroindoles Through p-TsOH Promoted Alkoxylation. *Tetrahedron Lett.* **2013**, *54*, 3176. (i) Noland, W. E.; Lanzatella, N. P.; Sizova, E. P.; Venkatraman, L.; Afanasyev, O. V. In Situ Vinylpyrrole Synthesis. Diels-Alder Reactions with Maleimides to Give Tetrahydroindoles. *J. Heterocycl. Chem.* **2009**, *46*, 503. (j) Peters, B. K.; Liu, J. G.; Margarita, C.; Rabten, W.; Kerdphon, S.; Orebom, A.; Morsch, T.; Andersson, P. G. Enantio- and Regioselective Ir-Catalyzed Hydrogenation of Di- and Trisubstituted Cycloalkenes. *J. Am. Chem. Soc.* **2016**, *138*, 11930. (k) Zhang, J. W.; Liu, X. W.; Gu, Q.; Shi, X. X.; You, S. L. Enantioselective Synthesis of 4,5,6,7-Tetrahydroindoles via Olefin Cross-Metathesis/Intramolecular Friedel-Crafts Alkylation Reaction of Pyrroles. *Org. Chem. Front.* **2015**, *2*, 476.

(4) (a) Mou, X. Q.; Xu, Z. L.; Wang, S. H.; Zhu, D. Y.; Wang, J.; Bao, W.; Zhou, S. J.; Yang, C.; Zhang, D. An Au(I)-catalyzed Rearrangement/cyclization Cascade Toward the Synthesis of 2-Substituted 1,4,5,6-Tetrahydrocyclopenta[b]pyrrole. *Chem. Commun.* **2015**, *51*, 12064. (b) Yoshida, M.; Maeyama, Y.; Al-Amin, M.; Shishido, K. Synthesis of Substituted 1,4,5,6-Tetrahydrocyclopenta-[b]pyrroles by Platinum-Catalyzed Cascade Cyclization/Ring Expansion of 2-Alkynyl-1-azaspiro[2.3]hexanes. *J. Org. Chem.* **2011**, *76*, 5813. (c) Rousseau, B.; Nydegger, F.; Gossauer, A.; BennuaSkalmowski, B.; Vorbruggen, H. *An Improved Method for the Preparation of N-Unsubstituted 1,4,5,6-Tetrahydrocyclopenta[b]pyrroles: Synthesis of an Azaprostacyclin Analogue and its 7-Cyano Derivative*; Synthesis-Stuttgart, 1996. (d) Muller, A.; Maier, A.; Neumann, R.; Maas, G. Alkoxycarbonylcarbene Transfer to Semicyclic Enaminones - A Route to Cyclopenta[b]pyrrole and Indole Ring Systems. *Eur. J. Org. Chem.* **1998**, *1998*, 1177.

(5) (a) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. Organic Synthesis Provides Opportunities to Transform Drug Discovery. *Nat. Chem.* **2018**, *10*, 383. (b) Campos, K. R.; Coleman, P. J.; Alvarez, J. C.; Dreher, S. D.; Garbaccio, R. M.; Terrett, N. K.; Tillyer, R. D.; Truppo, M. D.; Parmee, E. R. The Importance of Synthetic Chemistry in the Pharmaceutical Industry. *Science* **2019**, *363*, eaat0805. (c) Uehling, M. R.; King, R. P.; Krska, S. W.; Cernak, T.; Buchwald, S. L. Pharmaceutical Diversification via Palladium Oxidative Addition complexes. *Science* **2019**, *363*, 405.

(6) Ayala, C. E.; Dange, N. S.; Fronczek, F. R.; Kartika, R. Bronsted Acid Catalyzed Alpha'-Funztionalization of Silylenol Ethers with Indole. *Angew. Chem., Int. Ed.* **2015**, *54*, 4641.

(7) (a) Malone, J. A.; Van Houten, J. P.; Ganiu, M. O.; Nepal, B.; Kartika, R. Brønsted Acid Catalyzed Synthesis of Functionalized 1,4- and 1,6-Dicarbonyl Monosilyl Enol Ethers under Operationally Practical Conditions. *J. Org. Chem.* **2017**, *82*, 10659. (b) Stepherson, J. R.; Fronczek, F. R.; Kartika, R. An Expedient Synthesis of Functionalized 1,4-Diketone-derived Compounds via Silyloxyallyl Cation Intermediates. *Chem. Commun.* **2016**, *52*, 2300.

(8) (a) Paal, C. Ueber die Derivate des Acetophenonacetessigesters und des Acetonylacetessigesters. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2756. (b) Knorr, L. Synthese von Furfuranderivaten aus dem Diacetbernsteinsäureester. *Ber. Dtsch. Chem. Ges.* **1884**, *17*, 2863. (c) Amarnath, V.; Anthony, D. C.; Amarnath, K.; Valentine, W. M.; Wetterau, L. A.; Graham, D. G. Intermediates in the Paal-Knorr Synthesis of Pyrroles. *J. Org. Chem.* **1991**, *56*, 6924.

(9) See Supporting Information for detailed reaction optimizations.

(10) CCDC 1894940−1894943 contain the supplementary crystallographic data for compounds **7j**, **9a**, **13b**, and **13g**, respectively.

(11) Liu, C.; Oblak, E. Z.; Vander Wal, M. N.; Dilger, A. K.; Almstead, D. K.; MacMillan, D. W. C. Oxy-Allyl Cation Catalysis: An Enantioselective Electrophilic Activation Mode. *J. Am. Chem. Soc.* **2016**, *138*, 2134.

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Org. Lett. XXXX, XXX, XXX−XXX