Synthesis of Protoberberine Alkaloids by C–H Functionalization and Anionic Aza-6π-Electrocyclization: Dual Activity as AMPK Activators and Inhibitors

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ABSTRACT: 5'-Adenosine monophosphate-activated protein kinase (AMPK) plays a critical role in maintaining cellular energy homeostasis, and its activation has garnered attention for treating chronic metabolic diseases. Inhibitors of AMPK are underdeveloped but bear implications in treating cancers, controlling autophagy, and elderly wasting. Protoberberine alkaloids are typically regarded as AMPK activators. Herein, we report a modular synthesis strategy to access a collection of oxyberberine alkaloids, including the first synthesis of stepharotudine. *In vitro* assays reveal how subtle structural modifications can negate AMPK activation while conferring unprecedented inhibitory properties within the same class of compounds, which was previously unknown. Key steps in the synthesis include an oxidative Rh(III)-catalyzed C–H functionalization using electron-rich alkenes, NaH-mediated reductive *N*–O bond cleavage, and the first example of an anionic aza-6π-electrocyclization. Additionally, we provide mechanistic support for nucleophilic hydride transfer reactivity with NaH in DMF.

1. INTRODUCTION

Lifestyles that emphasize exercise and caloric restriction effect an increase in the activity of 5'-adenosine monophosphate-activated protein kinase (AMPK), a key regulator of metabolic and energy homeostasis.[1] This favorable enhancement curtails risks in developing chronic metabolic diseases like type-2 diabetes, obesity, non-alcoholic fatty liver disease (NAFLD), non-alcoholic steatoheptatitis (NASH), and cancers, even decelerating the aging process. As such, targeting AMPK is emerging as a promising avenue for therapeutic intervention — the aim being to emulate the low energy state that is conducive to combating diseases arising from the destabilizing imbalance between nutrient intake (i.e., high-calorie diets) and energy expenditure (i.e., increasingly sedentary routines).[2] Nearly all research efforts have focused on developing activators of AMPK, while their corresponding inhibitors remain underexplored. In fact, there are instances where AMPK promotes tumor cell survival and that its deficiency represses tumor growth.[2d,3] Therefore, the ability to regulate AMPK levels, including its inhibition, can have important implications for advancing cancer treatments. Controlling AMPK can also be developed into a strategy for modulating autophagy, a metabolic process that degrades damaged organelles and is associated with a wide variety of diseases.[4]

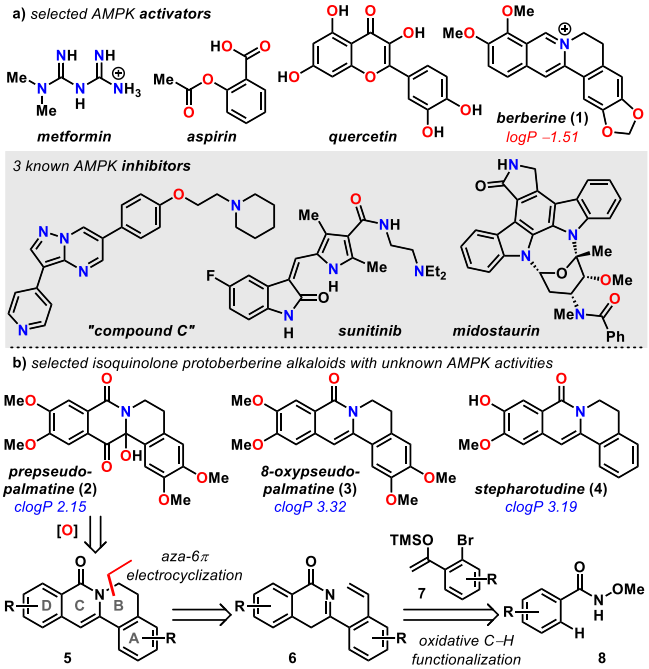

Figure 1. a) Examples of AMPK modulators. b) Our synthesis approach to protoberberine alkaloids with unknown AMPK activities.

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In contrast to the relatively abundant number of synthetic molecules and natural products that act as AMPK activators,[5] there are only three compounds known to inhibit AMPK,[3b] all of which are multikinase inhibitors (Figure 1a).

The Huang lab has a longstanding interest in understanding the mechanisms that underlie the therapeutic effects of AMPK modulators such as metformin and berberine (**1**, Figure 1a), and have uncovered a novel link between intestinal AMPK activation and brown adipose tissue (BAT) thermogenic regulation that is accompanied by modulation of the anti-microbial peptide (AMP)-controlled gut microbiota.[2c] Given how metabolic intermediates of berberine are similarly bioactive or may be the active forms following oral administration,[6] we hypothesized that the rarer biosynthetic precursors of berberine, such as prepseudopalmatine (**2**), 8-oxypseudopalmatine (**3**), and stepharotudine (**4**) could also exert AMPK modulation activity. Unlike berberine, protoberberine alkaloids resembling **2–4** make up minor components of the *Magnoliaceae*, *Ranunculaceae*, *Berberidaceae*, and *Menispermaceae* families of plants and are not accessible to the biomedical community. We have thus devised a convergent strategy to prepare natural and unnatural protoberberine analogs de novo highlighting methodologies developed in the Kou lab. The strength of this synthesis strategy compared to others[7] lies in its modularity in enabling derivatization of all four rings within the protoberberine scaffold. Compounds **2**–**4** and their derivatives were envisioned to arise from tetracyclic intermediate **5**. We imagined disconnecting ring B of the tetracycle through a novel 6π-aza-electrocyclic transform, thus simplifying the structure to dihydroisoquinolone **6**, which can be assembled directly from silyl enol ether **7** and hydroxamic ester **8** by oxidative C–H functionalization. This strategy led to the preparation of thirteen protoberberine-type alkaloids to survey the structure-activity relationship (SAR) with respect to AMPK modulation. We found that the absence of the cationic charge imposed by the quaternized nitrogen (*i.e.*, berberine) stymies AMPK activation ability, and the neutral protoberberines synthesized in this study represent novel examples of AMPK inhibitors.

2. RESULTS AND DISCUSSION

2.1. Synthesis of Protoberberine Alkaloids. To achieve a concise and modular synthesis strategy, we integrated an oxidative Rh(III)-catalyzed C–H functionalization (see SI) previously developed in the Kou lab that combines densely substituted enol silanes **7** with hydroxamic esters **8** to produce densely substituted 3-hydroxydihydroisoquinolones **9**, which upon treatment with aqueous HCl, eliminate water to form isoquinolones **10a-k** in 24–76% yields after two steps (Scheme 1a).[8] Given the multi-substitution patterns of the compound precursors, which are more complex than those reported in the original study, the reactivity and modest yields are remarkable. Our pursuit of oxidative C–H functionalization with enol silanes solves a major limitation in alkyne reactivity: enol silanes **7** are surrogates for terminal alkynes, which are poorly precedented in C–H functionalization,[9,10] with the exception of a recent study by the Pfizer Oncology group demonstrating success with propyne.[11] This methodology was effective in introducing multiple substitution patterns, including a bromide functional handle, into rings A and D. A ligand-free palladium-catalyzed cross-coupling was optimized to append a vinyl group, generating styrene derivatives **11** in up to 98% yields. The presence of an aldehyde in aryl bromide **10b** hampers productive cross-coupling, whereas aldoxime **10c** undergoes competitive palladium-catalyzed aldoxime rearrangement,[12] generating benzamide side-product **11c'** (37%) alongside the target Suzuki product (25%). These reactions set the stage for N-deprotection coupled to a novel anionic 6π-aza-electrocyclization. This process bypasses an otherwise multistep hydroboration/oxidation/activation/cyclization sequence[13] and directly furnishes the tetracyclic alkaloid core in 20–84% yields (Scheme 1b). In contrast to the syntheses of tetramethoxyoxyberberines (**3**) and (**14**) where NaH (3 equiv) mediated a tandem *N–O* cleavage[8,14] and 6π-aza-electrocyclization in 20 hours without additional additives, NaH induced *N–O* cleavage but only partial cyclization in all other examples. To circumvent this, we devised a one-pot protocol whereby KO*t*-Bu (0.5 equiv) is added following N-deprotection and additionally reacted for 18–22 hours to fully convert the reactant and complete the electrocyclization. Moderate to good yields (42–84%) were generally observed when the oxyberberine D-rings were electron-neutral (e.g., **4**, **16**, **17**) or electron poor (e.g., **18**, **19**). In contrast, lower isolated yields (15–31%) were obtained when the D-ring was substituted with electron-donating groups (i.e., **3**, **14**, **20**, **21**). The reduction in yield is attributed to sensitivity of the oxyberberine alkaloids to silica gel and alumina treatments, rather than inefficiencies in the electrocyclization reaction. In all cases, the electrocyclization produces high yields as determined by NMR analysis. Of note, the Suzuki reaction of aryl halide **10f** is accompanied by *N–O* cleavage, producing only deprotected isoquinolone **11f'** in 18% yield. Aryl halide **10k** with the three aryl halide bonds decomposes under the reaction conditions and therefore could not be converted to **11k**. In the cases of stepharotudine (**4**) and methoxystepharotudine **20**, their 5-exo-trig cyclization counterparts **4-iso** (2%) and **5-iso** (3%) were also formed as minor side-products and represent B-ring distortion analogs of stepharotudine.[15] Oxidation of 8-oxypseudopalmatine (**3**) led to the first preparation of the naturally occurring prepseudopalmatine (**2**) in 48% isolated yield.

2.2. AMPK Modulation and Structure-Activity Relationship. We initially targeted oxyberberine natural products **2** and **3** with higher oxygenation patterns because they have not been studied in a biological context and **2** had not been synthesized previously. In vitro kinase activity assays using the AMPK (α1/β1/γ1) kinase enzyme system (presented as IC_{50} data) and in vivo assays using the human intestinal epithelial cell line HT29[2c] revealed that altering the cationic isoquinolinium moiety characteristic of berberine (**1**) for the neutral isoquinolone stimies AMPK activation activity (Schemes 1b and 1c). Highly oxygenated alkaloids **2**, **3**, and **14** were poorly active or inactive in vitro. Removal of the two methoxy groups from the D ring resulted in a compound that inhibited AMPK with an IC_{50} of 85.3 μM. Fully reducing the enaminone motif of the

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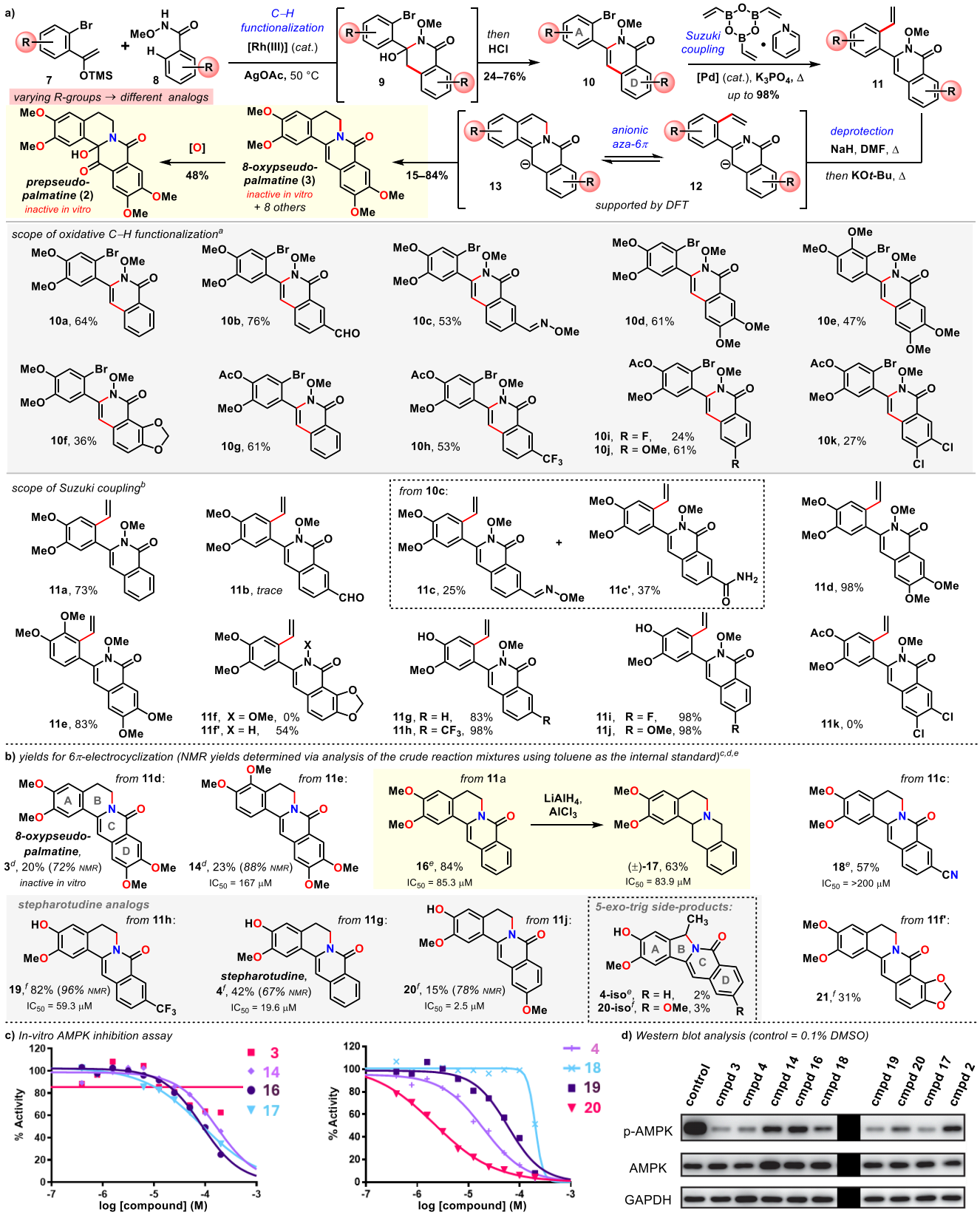

Scheme 1. a) Concise synthesis enabled by: i) oxidative Rh-catalysis and ii) anionic aza-6π-electrocyclization. Conditions: [a] $[Cp^*RhCl_2]_2$ (5 mol%), AgOAc (2.2 equiv), THF (0.2 M), 50 °C, 18 h; [b] $PdCl_2$ (5 mol%), boroxine (1.5 equiv), K_3PO_4 (3 equiv), 1,4-dioxane/H_2O (0.1 M), 130 °C, 18 h; [c] % conv. by NMR. [d] NaH (3 equiv), 130 °C, 20 h; [e] NaH (2 equiv), 130 °C, 3 h, then KO*t*-Bu (0.5 equiv), 130 °C, 18 h; [f] NaH (3 equiv), 130 °C, 3 h, then KO*t*-Bu (0.5 equiv), 130 °C, 20 h. b) IC_{50} efficacies for AMPK(α1/β1/γ1) and discovery of stepharotudine analogs as novel AMPK inhibitors. c) AMPK inhibition assays; IC_{50} data are extracted and presented with compounds in Scheme 1b. d) Western blot analysis of phosphorylated AMPK, total AMPK, and glyceraldehyde 3-phosphate dehydrogenase; control = 0.1% DMSO.

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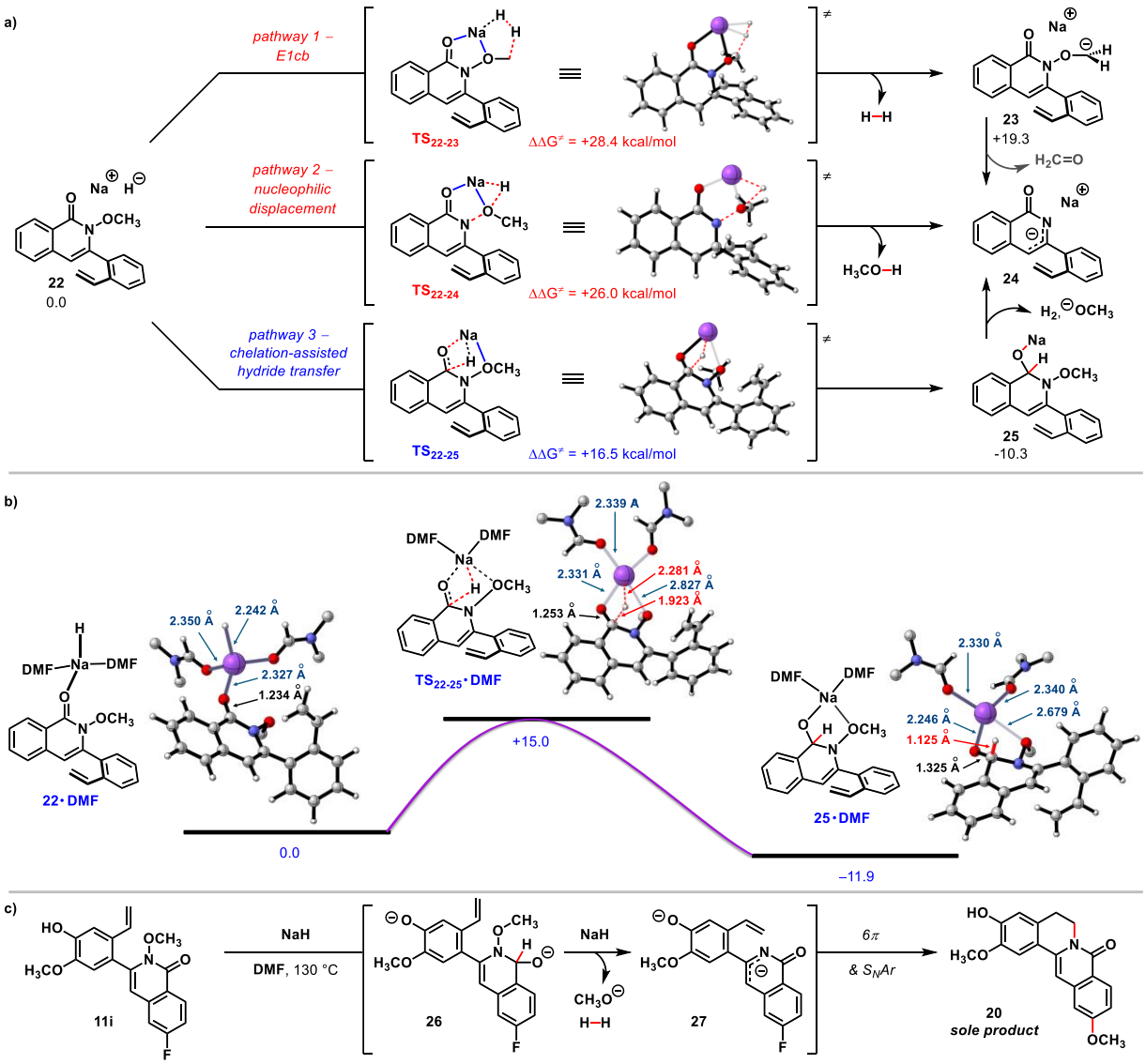

Scheme 2. a) Mechanisms of NaH-mediated N–O cleavage computed by DFT at the B3LYP/6-311+G(2d,p) level of theory with implicit solvation (CPCM) by DMF at 428.15 K (See SI for complete energy profiles); Free energies expressed in kcal/mol. b) Chelation-assisted nucleophilic hydride delivery with both implicit (CPCM, DMF) and explicit solvation. Methyl hydrogens are omitted for clarity. c) Observed experimental S_NAr reactivity consistent with hydride transfer pathway.

isoquinolone resulted in racemic tertiary amine **17** with similar inhibitory potential. Rendering the D-ring electron-deficient with a cyano group (e.g., **18**) gave an inactive compound. Stepharotudine-type compounds **4**, **19**, and **20** with guaiacolic A-rings exerted the greatest activities with unnatural **20** displaying an IC_{50} of 2.5 μM. This data suggests that the protoberberine derivatives examined in this study exhibit a distinct mechanism of action compared to berberine (**1**) and can directly inhibit AMPK. Western blot analysis additionally supports the inhibitory activities of the protoberberine analogs against phosphorylated AMPK (Scheme 1d). While 8-oxypseudopalmatine (**3**) was inactive *in vitro*, it produced the greatest inhibition when subjected to whole cells by Western blot. Presumably, demethylation of one or more of the methoxy substituents in cells generated a guaicolic derivative that exerts greater potency. We were able to test the B-ring distortion analogs (**4-iso** and **20-iso**) by Western blot analysis and found them to also inhibit p-AMPK (see SI). Thus, deviating from planarity does not substantially impact AMPK modulation. Collectively, the data suggest that the A-ring guaiacolic –OH group and an electron-rich D-ring are important in enhancing AMPK inhibition. Our study is the first to uncover the AMPK inhibition potential of protoberberines that have long been studied for their activation properties, while elucidating structural features that govern bioactivity.

2.3. Mechanism of *N*-Deprotection and Aza-6π-Electrocyclization. The *N*-methoxy substituent of the hydroxamic esters (**8**) is important in facilitating directed C–H activation[16] and doubles as an amide protecting group. *N*-Deprotection followed by 6π-aza-electrocyclization provides direct and facile entry into the target oxyberberine scaffold. We evaluated three possible mechanistic scenarios by density functional theory (DFT)

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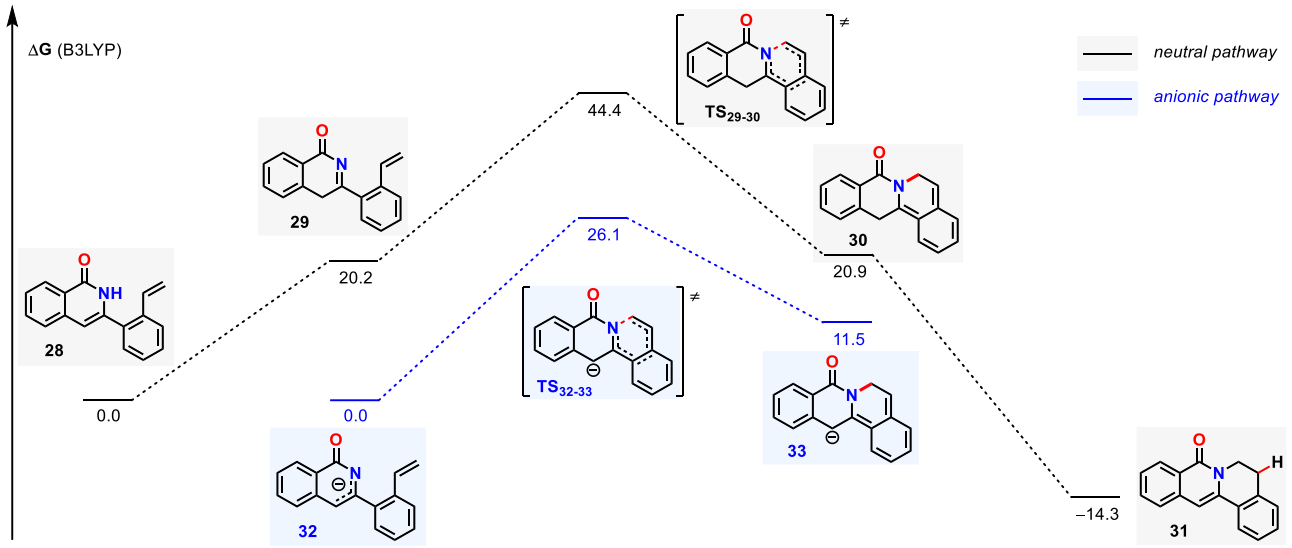

Figure 2. The free energy (kcal/mol) profile for the aza-6π-electrocyclization at the B3LYP/6-311++G(d,p) level of theory with implicit solvation (CPCM) by DMF.

via Gaussian 16[17] at the B3LYP/6-311+G(2d,p) level of theory,[18–21] including a solvent correction using the CPCM method[22] with dimethylformamide as the solvent (Figure 2a). The pathway where NaH acts as a base, participating in an E1cb elimination reaction via rate-limiting **TS$_{22\text{-}23}$** to release conjugate base **23** and formaldehyde as the byproduct (Scheme 2a, pathway 1) occurs with a rate-limiting barrier of 28.4 kcal/mol. Subsequent fragmentation with loss of formaldehyde generates quinolone anion **24** (see SI for full energy diagram and mechanism). If this pathway was operative, we expected to observe side-products originating from Friedel–Crafts reactivity with formaldehyde,[23] especially under high temperature conditions. However, Friedel–Crafts-type products were never detected over the course of our studies. Although there are no practical examples of NaH behaving in a nucleophilic displacement (S_N2-type) reaction,[14] a transition state (**TS$_{22\text{-}24}$**, $\Delta\Delta G^{\neq}$ = 26.0 kcal/mol) was located where the hydride engages in an S_N2-type fashion to cleave the *N*–*O* bond, directly forming quinolone anion **24** (pathway 2). We posited that NaH can potentially engage the carbonyl in a reduction manner,[24] and computed **TS$_{22\text{-}25}$** with a significantly lower barrier of 16.5 kcal/mol, to arrive at tetrahedral intermediate **25**, which then collapses ($\Delta\Delta G_{25\text{-}24}^{\neq}$ = +6.0 kcal/mol, see SI) to the same aromatic anion **24** (pathway 3). Such a nucleophilic hydride transfer by NaH would represent previously undisclosed reduction reactivity occurring under additive-free conditions. Previous DFT calculations to understand NaH-mediated nucleophilicity explicitly included two molecules of solvent ligating sodium;[24b] therefore, pathway 3 was also computed via both implicit (CPCM with DMF) and explicit solvation. The inclusion of two molecules of DMF supporting sodium provided additionally stabilization to both the rate-determining hydride-delivery transition state (**TS$_{22\text{-}25}$·DMF**) ($\Delta\Delta G^{\neq}$ = 15.0 kcal/mol, Scheme 2b) and the resulting tetrahedral intermediate **25·DMF**. This unusual nucleophilic hydride delivery is likely proceeding under chelation assistance by the *N*-methoxylactam motif and the analogous transition state structure for NaH-mediated hydride transfer to formaldehyde lacking a chelating group could not be located (see SI). When fluorinated *N*-methoxyisoquinolone **11i** was subjected to deprotection/aza-6π-electrocyclization, remote *N*-to-*C* migration of the methoxy group ensued, leading to the isolation of methoxy-substituted oxyberberine **20** as the sole product, presumably through the intermediacy of **26** and **27** (Scheme 2c). Supportive of pathway 3 (Scheme 2a), this outcome is rationalized to occur through a nucleophilic aromatic substitution by the methoxide anion ejected from *N*-deprotection.

The necessity for base suggests that the anionic attributes of intermediates **12** (Scheme 1a), **24** (Scheme 2a), and **27** (Scheme 2b) may be facilitating the subsequent 6π-aza-electrocyclization. While anionic aza-Cope[25] and anionic 4π- electrocyclic[26] reactions have been documented in the literature, our study highlights the first example of an anionic 6π-electrocyclic ring closure. We computed the Gibbs free energy profiles for both the anionic and neutral pathways by DFT and found the anion acceleration effect to be significant (Figure 2). The barrier to anionic 6π-aza-electrocyclization is 18.3 kcal/mol lower in energy compared to the neutral pathway when examining the transition state energies of **TS$_{29\text{-}30}$** and **TS$_{32\text{-}33}$** ($\Delta\Delta G^{\ddagger}$ = 44.4 – 26.1 = 18.3 kcal/mol), the origin of which is rationalized to be ground state destabilization akin to the anionic oxy-Cope[27], anionic oxy-Claisen[28] and carbanionic Claisen[29] rearrangements. In the present aza-electrocyclization, isomerization of the enamide component of isoquinolone **28** to acylimine **29** is 20.2 kcal/mol uphill by DFT, a consequence that is negated upon deprotonation to anion **32**. In other words, the anionic path effectively bypasses the tautomerization step required in the neutral path. The annulation process to tetracycle **33** is thermodynamically uphill, and the driving force is attributed to protonation by solvent DMF. This and the reversible nature of the electrocyclization is corroborated by experimental mechanistic studies conducted in deuterated DMF (Scheme 3). In most cases, KO*t*-Bu is necessary

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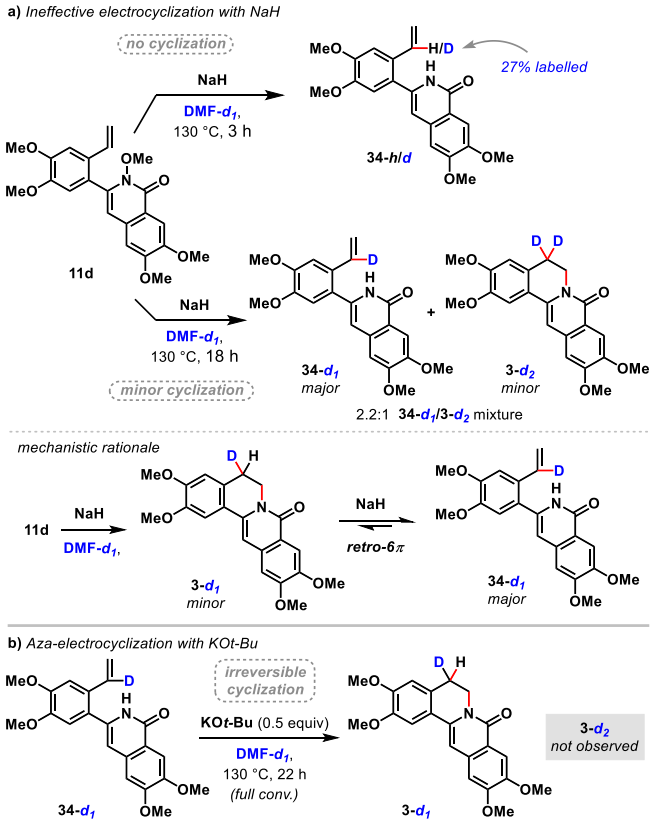
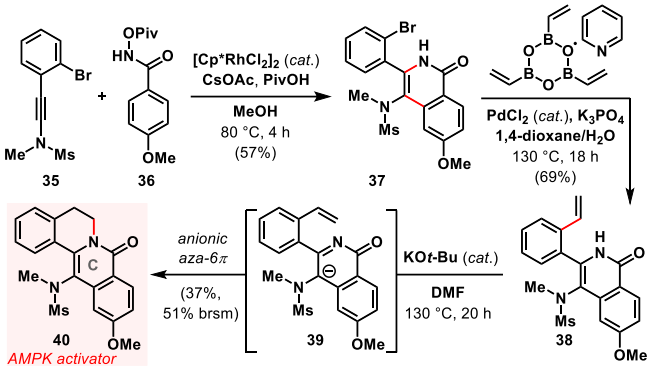


Scheme 3. The roles of bases in sequential deprotection/aza-6π-electrocyclization.

to effect 6π-electrocyclic ring closure following NaH-mediated *N–O* bond cleavage. When cyclization precursor **11d** was subjected to NaH in deuterated DMF, deprotected isoquinolone **34** was observed as the sole product with 27% deuterium-labeling at the internal site of the alkene (Scheme 3a). Prolonged heating led to a mixture of monodeuterated isoquinolone **34-*d*$_1$** and dideuterated 8-oxypseudopalmatine **3-*d*$_2$** in a 2.2:1 ratio in favor of the acyclic intermediate. Incorporation of deuterium into the alkene is rationalized to occur by 6π-aza-electrocyclization, deuteration by DMF-*d*$_1$, and base-mediated 6π-electrocyclic ring-opening or elimination. Extended exposure to NaH and heat would promote cyclization to dideuterated **3-*d*$_2$**. These observations are consistent with the DFT calculations that suggest aza-electrocyclization to be endergonic. Under KO*t*-Bu catalysis conditions, electrocyclic ring-closure to 8-oxypseudopalmatine **3-*d*$_1$** is irreversible due to KO*t*-Bu's lower basicity (Scheme 3b). In contrast to dideuteration of the tetracycle, only monodeuterated **3-*d*$_1$** is generated from protonation by *t*-BuOH or the isoquinolone that are more acidic than DMF. Past mechanistic studies on reactions involving KO*t*-Bu in DMF generally invoke single-electron transfer pathways;[30] however, the current deprotection/6π-aza-electrocyclization sequence is better consistent with a polar 2-electron pathway, proceeding under air, inert atmosphere, and in the presence of TEMPO (see SI). The base-mediated anionic 6π-aza-electrocyclization reported herein is distinct from and complementary to the acid-mediated 6π-aza-electrocyclization for benzoquinoline synthesis[31] and C–H alkenylation/6π-electrocyclization cascade for dihydropyridine synthesis.[32]



Scheme 4. C–H functionalization/Suzuki/anionic aza-6π-electrocyclization sequence en-route to aminoprotoberberine with C-ring derivatization.

2.4. Modification of the Protoberberine C-Ring: Restoration of AMPK Activation Activity. Contrary to previous reports of protoberberine synthesis,[8] the present modular and convergent strategy stands out as the sole method capable of modifying all four rings of the tetracyclic scaffold, thereby facilitating the preparation of diverse analogs. Schemes 1a and 1b show rings A and D being modified by starting with various readily accessible silyl enol ethers **7** and hydroxamic esters **8** as coupling partners. While this study focused on introducing a vinyl group by Suzuki cross-coupling, incorporating substituted alkenes would generate novel B-ring analogs. Distorted B-ring analogs **4-iso** and **20-iso** were formed as minor side products and isolated for bioassays; however, they can be deliberately synthesized by Markovnikov hydration of the vinyl group,[33] followed by cyclization. The oxidative C–H functionalization of *N*-methoxybenzamides with silyl enol ethers was necessary to access natural protoberberines without substitution on the alkene of the C-ring. This strategy is also amenable in employing related C–H functionalization reactions with the broader class of internal alkynes to generate C-ring analogs.[34] This is exemplified in the synthesis of aminoprotoberberine **40** (Scheme 4). The annulative coupling between ynamide **35** and *N*-pivaloylbenzamide **36** yields aminoisoquinolone **37** in 57% yield.[35] Despite the additional sulfonamide group, Suzuki cross-coupling to append on the vinyl substituent proceeds in 69% yield. Since the *N–O* bond is cleaved in the C–H functionalization step, aza-6π-electrocyclization can be initiated by treating isoquinolone **38** with catalytic KO*t*-Bu, presumably forming anionic intermediate **39** en-route to the target tetracycle (**40**) in 37% yield (51% brsm). Western blot analysis revealed that C-ring modification with a sulfonamide group restored AMPK activation (see SI).

3. CONCLUSIONS

Utilizing C–H functionalization and anionic aza-6π-electrocyclization strategies developed in our lab, we have orchestrated a concise and convergent strategy that generates diverse protoberberine natural and unnatural products with derivatization at all the A, B, C and D rings. De-

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rivatives with electron-donating groups on the D-ring tend to be unstable to purification. In the process, we have uncovered nucleophilic hydride reactivity elicited by NaH in DMF and in the absence of external additives such as NaI. The natural product stepharotudine (**4**) was synthesized for the first time. Traditionally, protoberberine derivatives have been developed and studied under the presumption that they act as AMPK activators, as evidenced by several studies[2c,6,36] and patents[37] focused on their potential use in treating diabetes. However, our findings challenge this paradigm by demonstrating that many protoberberines are AMPK inhibitors, a previously unappreciated property. This insight opens new avenues for the biomedical relevance of these compounds, particularly in areas where AMPK inhibition could be therapeutically beneficial. Furthermore, we found that incorporating a sulfonamide group into the C-ring restores AMPK activation, providing a novel insight for future explorations of berberine-derived AMPK modulators. There is currently substantial interest in advancing AMPK activators for obesity, diabetes, and liver illnesses, and we envision that the advancement of AMPK inhibitors will have novel therapeutic applications in cancer treatment, controlling autophagy, and elderly wasting.

ASSOCIATED CONTENT

Supporting Information.

The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

Procedures including Preparation of Substrates, Characterization Data, Biological Assays, Density Functional Theory (DFT) studies, and NMR Spectra.

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Author Contributions

The manuscript was written through contributions of all authors. ǁThese authors contributed equally.

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REFERENCES

(1) (a) Spaulding, H. R.; Yan, Z. AMPK and the Adaptation to Exercise. *Annu. Rev. Physiol.* **2022**, *84*, 209–227. DOI: 10.1146/annurev-physiol-060721-095517 (b) Steinber, G.R.; Carling, D. AMP-activated protein kinase: the current landscape for drug development. *Nat. Rev. Drug Discov.* **2019**, *18*, 527–551. DOI: 10.1038/s41573-019-0019-2

(2) (a) Pollard, A. E.; Martins, L.; Muckett, P. J.; Khadayate, S.; Bornot, A.; Clausen, M.; Admyre, T.; Bjursel,l M.; Fiadeira, R.; Wilson, L.; Whilding, C.; Kotiadis, V. N.; Duchen, M. R.; Sutton, D.; Penfold, L.; Sardini, A.; Bohlooly-Y, M.; Smith, D. M.; Read, J. A.; Snowden,M. A.; Woods, A.; Carling, D. AMPK activation protects against diet induced obesity through Ucp1-independent thermogenesis in subcutaneous white adipose tissue. *Nat. Metab.* **2019**, *1*, 340–349. DOI: 10.1038/s42255-019-0036-9 (b) Liu, Y.; Jurczak,M. J.; Lear, T. B.; Lin, B.; Larsen,M. B.; Kennerdell, J. R.; Chen, Y.; Huckestein, B. R.; Nguyen, M. K.; Tuncer, F.; Jiang, Y.; Monga, S. P.; O'Donnell, C. P.; Finkel, T.; Chen, B. B.; Mallampalli, R. K. A Fbxo48 inhibitor prevents pAMPKα degradation and ameliorates insulin resistance. *Nat. Chem. Bio.* **2021**, *17*, 298–306. DOI: 10.1038/s41589-020-00723-0 (c) Zhang, E.; Jin, L.; Wang, Y.; Tu, J.; Zheng, R.; Ding, L.; Fang, Z.; Fan, M.; Al-Abdullah, I.; Natarajan, R.; Ma, K.; Wang, Z.; Riggs, A. D.; Shuck, S. C.; Yang, L.; Huang, W. Intestinal AMPK modulation of microbiota mediates crosstalk with brown fat to control thermogenesis. *Nat. Commun*. **2022**, *13*, 1135. DOI: 10.1038/s41467-022-28743-5 d) Steinberg, G. R.; Hardie, D. G. New insights into activation and function of the AMPK. *Nat. Rev. Mol. Cell. Biol.* **2023**, *24*, 255. DOI: 10.1038/s41580-022-00547-x

(3) (a) Jeon, S.-M.; Chandel, N. S.; Hay, N. AMPK regulates NADPH homeostasis to promote tumour cell survival during energy stress. *Nature* **2012**, 485, 661–665. DOI: 10.1038/nature11066 (b) Jeon, S.-M.; Hay, N. The double-edged sword of AMPK signaling in cancer and its therapeutic implications. *Arch. Pharm. Res.* **2015**, *38*, 346–357. DOI: 10.1007/s12272-015-0549-z c) Dasgupta, B.; Chhipa, R. R. Evolving Lessons on the Complex Role of AMPK in Normal Physiology and Cancer. *Trends Pharmacol. Sci.* **2016**, *37*, 192–206. DOI: 10.1016/j.tips.2015.11.007 d) Eichner, L. J.; Brun, S. N.; Herzig, S.; Young, N. P.; Curtis, S. D.; Shackelford, D. B.; Shokhirev, M. N.; Leblanc, M.; Vera, L. I.; Hutchins, A.; Ross, D. S.; Shaw, R. J.; Svensson, R. U. Genetic Analysis Reveals AMPK Is Required to Support Tumor Growth in Murine Kras-Dependent Lung Cancer Models. *Cell Metab.* **2019**, *29*, 285–302.e7. DOI: 10.1016/j.cmet.2018.10.005 e) Sadria, M.; Seo, D.; Layton, A. T. The mixed blessing of AMPK signaling in Cancer treatments. *BMC Cancer* **2022**, *22*, 105. DOI: 10.1186/s12885-022-09211-1

(4) (a) Whitmarsh-Everiss, T.; Laraia, L. Small molecule probes for targeting autophagy. *Nat. Chem. Biol.* **2021**, *17*, 653–664. DOI: 10.1038/s41589-021-00768-9 (b) Barnaba, C.; Broadbent, D. G.; Kaminsky, E. G.; Perez, G. I.; Schmidt, J. C. AMPK regulates phagophore-to-autophagosome maturation. *J. Cell. Biol.* **2024**, *223*, e202309145. DOI: 10.1083/jcb.202309145

(5) Hardie, D. G. AMPK: a target for drugs and natural products with effects on both diabetes and cancer. *Diabetes* **2013**, *62*, 2164–72. DOI: 10.2337/db13-0368

(6) (a) Cao, S.; Zhou, Y.; Xu, P.; Wang, Y.; Yan, J.; Bin, W.; Qiu, F.; Kang, N. Berberine metabolites exhibit triglyceride-lowering effects via activation of AMP-activated protein kinase in Hep G2 cells. *J. Ethnopharmacol*. **2013**, *149*, 576–582. DOI: 10.1016/j.jep.2013.07.025 (b) Zhou, Y.; Cao, S.; Wang, Y.; Xu, P.; Yan, J.; Bin, W.; Qiu, F.; Kang, N. Berberine metabolites could induce low density lipoprotein receptor up-regulation to exert lipid-lowering effects in human hepatoma cells. *Fitoterapia* **2014**, *92*, 230–7. DOI: 10.1016/j.fitote.2013.11.010

(7) (a) Le, T. N.; Gang, S. G.; Cho, W.-J. A Versatile Total Synthesis of Benzo[c]phenanthridine and Protoberberine Alkaloids Using Lithiated Toluamide–Benzonitrile Cycloaddition. *J. Org. Chem.* **2004**, *69*, 2768–2772. DOI: 10.1021/jo035836+ (b) Van, H. T. M.; S. H. Yang,; Khadka, D. B.; Kim, Y.-C.; Cho, W.-J. Total synthesis of 8-oxypseudopalmatine and 8-oxypseudoberberine via ring-closing metathesis *Tetrahedron* **2009**, *65*, 10142–10148. DOI: 10.1016/j.tet.2009.10.027 (c) Gatland, A. E.; Pilgram, B. S.;

https://doi.org/10.26434/chemrxiv-2025-78nhj **ORCID:** https://orcid.org/0000-0002-4676-8846 Content not peer-reviewed by ChemRxiv. **License:** CC BY 4.0

Procopiou, P. A.; Donohue, T. J. Short and Efficient Syntheses of Protoberberine Alkaloids using Palladium-Catalyzed Enolate Arylation. *Angew. Chem. Int. Ed.* **2014**, *53* (52), 14555–14558. DOI: 10.1002/anie.201409164 *Angew. Chem.* **2014**, *126*, 14783–14786. DOI: 10.1002/ange.201409164 (d) Jayakumar, J.; Cheng, C.-H. Direct Synthesis of Protoberberine Alkaloids by Rh-Catalyzed C–H Bond Activation as the Key Step. *Chem. Eur. J.* **2016**, *22* (5), 1800–1804. DOI: 10.1002/chem.201504378 (e) Zhou, S.; Tong, R. A General, Concise Strategy that Enables Collective Total Syntheses of over 50 Protoberberine and Five Aporhoeadane Alkaloids within Four to Eight Steps. *Chem. Eur. J.* **2016**, *22* (21), 7084–7089. DOI: 10.1002/chem.201601245 (f) Li, S.; Nie, H.; Duan, M.; Wang, W.; Zhu, C.; Song, C. Construction of a Protoberberine Alkaloid Skeleton via the Palladium-Catalyzed α-Arylation–Amide Formation Cascade. *Org. Lett.* **2021**, *23* (24), 9631–9634. DOI: 10.1021/acs.orglett.1c03871 (g) Tajiri, M.; Yamada, R.; Hotsumi, M.; Makabe, K.; Konno, H. The total synthesis of berberine and selected analogues, and their evaluation as amyloid beta aggregation inhibitors. *Eur. J. Med. Chem.* **2021**, *215*, 113289. DOI: 10.1016/j.ejmech.2021.113289 (h) Sun, Z.; Zhang, X.; Fu, J.; Zhang, L.; Cheng, M.; Yang, L.; Liu, Y. Collective Syntheses of 8-Oxoprotoberberines via Sequential $In(OTf)_3$-Catalyzed Cyclization and $Pd(OAc)_2$-Catalyzed Heck Coupling. *J. Org. Chem.* **2023**, *88* (11), 7179–7187. DOI: 10.1021/acs.joc.3c00419 (i) Song, Y.; Li, R.; Bai, J.; Li, X.; Zhou, S.; Zhang, Y. Carboxylic Acid-Enabled Vinylene Transfer Reaction by Co(III) Catalyst: Scope and Applications to the Five-Step Total Synthesis of Protoberberine Alkaloids Containing Free Hydroxyl Group without Protection. *J. Org. Chem.* **2024**, *89* (5), 3238–3250. DOI: 10.1021/acs.joc.3c02707

(8) Kou, X.; Kou, K. G. M. α-Arylation of Silyl Enol Ethers via Rhodium(III)-Catalyzed C–H Functionalization. *ACS Catal*. **2020**, *10* (5), 3103–3109. DOI: 10.1021/acscatal.9b05622

(9) Cao, Y.; Kou, K. G. M. in Handbook of C–H Functionalization, First Edition (Ed.: D. Maiti).; Rhodium-Catalyzed Heterocycle Synthesis by C–H Functionalization; John Wiley & Sons, Ltd, 2022; pp. 1–39. DOI: 10.1002/9783527834242.chf0111

(10) Xu, M. Y.; Yang, C.; Jiang, W. T.; Xiao, B. Synthesis and Application of Heterocyclic Germatranes via Rhodium-Catalyzed Directed C–H Activation/Annulation with Alkynyl Germatranes and Palladium-Catalyzed Cross-Coupling. *Adv. Synth. Catal*. **2020**, *362* (8), 1706–1711. DOI: 10.1002/adsc.201901633

(11) Barber, J. S.; Kong, D.; Li, W.; McAlpine, I. J.; Nair, S. K.; Sakata, S. K.; Sun, N.; Patman, R. L. Rhodium(III)-Catalyzed C–H Activation: Annulation of Petrochemical Feedstocks for the Construction of Isoquinolone Scaffolds. *Synlett* **2021**, *32*, 202–206. DOI: 10.1055/s-0040-1706548

(12) Menéndez-Rodríguez, L.; Tomás-Mendivil, E.; Francos, J.; Nájera, C.; Crochet, P.; Cadierno, V. Palladium(II) complexes with a phosphino-oxime ligand: synthesis, structure and applications to the catalytic rearrangement and dehydration of aldoximes. *Catal. Sci. Technol.* **2015**, *5*, 3754–3761. DOI: 10.1039/c5cy00413f

(13) Barcan, G. A.; Patel, A.; Houk, K. N.; Kwon, O. A Torquoselective 6π Electrocyclization Approach to Reserpine Alkaloids. *Org. Lett.* **2012**, *14* (21), 5388–5391. DOI: 10.1021/ol302265z

(14) Lu, S.; Lin, Y.; Zhong, H.; Zhao, K.; Huang, J. A practical one-pot procedure for the synthesis of N–H isoquinolones. *Tetrahedron Lett*. **2013**, *54* (15), 2001–2005. DOI: 10.1016/j.tetlet.2013.02.003

(15) (a) Huigens III, R. W.; Morrison, K. C.; Hicklin, R. W.; Flood Jr, T. A.; Richter, M. F.; Hergenrother, P. J. A ring-distortion strategy to construct stereochemically complex and structurally diverse compounds from natural products. *Nat. Chem*. **2013**, *5*, 195–202. DOI: 10.1038/nchem.1549; (b) Li, Y.; Cheng, S.; Tian, Y.; Zhang, Y.; Zhao, Y. Recent ring distortion reactions for diversifying complex natural products. *Nat. Prod. Rep*. **2022**, *39* (10), 1970–1992. DOI: 10.1039/D2NP00027J

(16) Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. A Simple and Versatile Amide Directing Group for C–H Functionalizations. *Angew. Chem. Int. Ed*. **2016**, *55* (36), 10578–10599. DOI: 10.1002/anie.201600791

(17)Gaussian 16, Revision C.01, Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Bar-one, V.; Petersson, G. A.; Nakatsuji, H.; Li, X.; Caricato, M.; Marenich, A. V.; Bloino, J.; Janesko, B. G.; Gomperts, R.; Mennucci, B.; Hratchian, H. P.; Ortiz, J. V.; Izmaylov, A. F.; Sonnenberg, J. L.; Williams-Young, D.; Ding, F.; Lipparini, F.; Egidi, F.; Goings, J.; Peng, B.; Petrone, A.; Henderson, T.; Ranasinghe, D.; Zakrzewski, V. G.; Gao, J.; Rega, N.; Zheng, G.; Liang, W.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Throssell, K.; Montgom-ery, J. A.; Jr., Peralta, J. E.; Ogliaro, F.; Bearpark, M. J.; Heyd, J. J.; Brothers, E. N.; Kudin, K. N.; Staroverov, V. N.; Keith, T. A.; Koba-yashi, R.; Normand, J.; Raghavachari, K.; Rendell, A. P.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Millam, J. M.; Klene, M.; Adamo, C.; Cammi, R.; Ochterski, J.W.; Martin, R.L.; Morokuma, K.; Farkas, O.; Foresman, J. B. and Fox, D. J. Gsussian, Inc., Wallingford CT, 2016

(18) Becke, A. D. Density-Functional Thermochemistry. III. The Role of Exact Exchange. *J. Chem. Phys*. **1993**, *98*, 5648–5652. DOI: 10.1063/1.464913

(19) Lee, C.; Yang, W.; Parr, R. G. Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density. *Phys. Rev. B* **1988**, *37*, 785–789. DOI: 10.1103/physrevb.37.785

(20) Vosko, S. H.; Wilk, L.; Nusair, M. Accurate spin-dependent electron liquid correlation energies for local spin density calculations: a critical analysis. *Can. J. Phys.* **1980**, *58*, 1200–1211. DOI: 10.1139/p80-159

(21) Stephens, P. J.; Devlin, F. J.; Chabalowski, C. F.; Frisch, M. J. Ab Initio Calculation of Vibrational Absorption and Circular Dichroism Spectra Using Density Functional Force Fields. *J. Phys. Chem.* **1994**, *98*, 11623–11627. DOI: 10.1021/j100096a001

(22) Takano, Y.; Houk, K. N. Benchmarking the Conductor-like Polarizable Continuum Model (CPCM) for Aqueous Solvation Free Energies of Neutral and Ionic Organic Molecules. *J. Chem. Theory Comput.* **2005**, *1*, 70–77. DOI: 10.1021/ct049977a

(23) (a) Sun, H.-B.; Hua, R.; Yin, Y. An efficient synthesis of diarylmethanes via InCl3·4H2O-catalyzed dehydration of electron-rich arenes with trioxane. *Tetrahedron Lett.* **2006**, *47*, 2291–2294. DOI: 10.1016/j.tetlet.2006.02.020; (b) Li, Z. X.; Duan, Z.; Wu, Y. J. $FeCl_3$ catalyzed diarylmethanes formations. *Chin. Chem. Lett.* **2009**, *20*, 511–513. DOI: 10.1016/j.cclet.2009.01.033; c) Crowley III, R.; Lujan, B.; Martinez, A.; Manasi, R.; DeBow, J. D.; Kou, K. G. M. A Fenton Approach to Aromatic Radical Cations and Diarylmethane Synthesis. *J. Org. Chem.* **2023**, *88*, 15060–15066. DOI: 10.1021/acs.joc.3c01505

(24) (a) Too, P. C.; Chan, G. H.; Tnay, Y. L.; Hirao, H.; Chiba, S. Hydride Reduction by a Sodium Hydride-Iodide Composite. Angew. Chem. Int. Ed. 2016, 55 (11), 3719–3723. DOI: 10.1002/anie.201600305; Angew. Chem. 2016, 128 (11), 3783–3787. DOI: 10.1002/ange.201600305 (b) Hong, Z.; Ong, D. Y.; Muduli, S. K.; Too, P. C.; Chan, G. H.; Tnay, Y. L.; Chiba, S.; Nishiyama, Y.; Hirao, H.; Soo, H. S. Understanding the origins of nucleophilic hydride reactivity of a sodium hydride-iodide composite. *Chem. Eur. J.* **2016**, *22*, 7108–7114. DOI: 10.1002/chem.201600340

(25) (a) Das, P.; Delost, M. D.; Quresh, M. H.; Bao, J.; Fell, J. S.; Houk, K. N.; Njardarson, J. T. Dramatic Effect of γ-Heteroatom Dienolate Substituents on Counterion Assisted Asymmetric Anionic Amino-Cope Reaction Cascades. *J. Am. Chem. Soc.* **2021**, 143 (15), 5793–5804. DOI: 10.1021/jacs.1c00745; (b) Qureshi, M. H.; Njardarson, J. T. Anionic Amino-Cope Rearrangement Cascade Synthesis of 2,4-Substituted Benzoate Esters from Acyclic Building Blocks. *Org. Lett.* **2022**, 24 (43), 7978–7982. DOI: 10.1021/acs.orglett.2c03134

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(26) (a) Kametani, T.; Tsubuki, M.; Nemoto, H.; Suzuki, K. Concerted ring-opening reaction of cyclobutenes. The extraordinary accelerating effects of arylsulfoxy and sulfonyl carbanion substituents. *J. Am. Chem. Soc*. **1981**, *103* (5), 1256–1258. DOI: 10.1021/ja00395a063; b) Paquette, L. A. Cascade Rearrangements Following Twofold Addition of Alkenyl Anions to Squarate Esters. *Eur. J. Org. Chem*. **1998**, *1998* (9), 1709–1728. DOI: 10.1002/(SICI)1099-0690(199809)1998:9<1709::AID-EJOC1709>3.0.CO;2-S; (c) Paquette, L. A.; Geng, F. Applications of the Squarate Ester Cascade to the Expeditious Synthesis of Hypnophilin, Coriolin, and Ceratopicanol. *J. Am. Chem. Soc*. **2002**, *124* (31), 9199–9203. DOI: 10.1021/ja020474t

(27) (a) Evans, D. A.; Golob, A. M. [3,3]Sigmatropic rearrangements of 1,5-diene alkoxides. Powerful accelerating effects of the alkoxide substituent. *J. Am. Chem. Soc*. **1975**, *97* (16), 4765–4766. DOI: 10.1021/ja00849a054; (b) Evans, D. A.; Baillargeon, D. J. Alkoxide substituent effects on carbon—carbon bond homolysis. *Tetrahedron Lett*. **1978**, *19* (36), 3319–3322. DOI: 10.1016/S0040-4039(01)85627-6; c) Steigerwald, M. L.; Goddard III, W, A,; Evans, D. A. Theoretical studies of the oxy anionic substituent effect. *J. Am. Chem. Soc*. **1979**, *101* (8), 1994–1997. DOI: 10.1021/ja00502a011

(28) (a) Denmark, S. E.; Harmata, M. A. Carbanion-Accelerated Claisen Rearrangements. *J. Am. Chem. Soc*. **1982**, *104*, 4972–4974. DOI: 10.1021/ja00382a051; (b) Denmark, S. E.; Harmata, M. A. Carbanion-accelerated Claisen rearrangements. 2. Studies on internal asymmetric induction. *J. Org. Chem*. **1983**, *48* (19), 3369–3370. DOI: 10.1021/jo00167a058; (c) Denmark, S. E.; Harmata, M. A. Carbanion-accelerated Claisen rearrangements 3. Vicinal quaternary centers. *Tetrahedron Lett*. **1984**, *25*, 1543. DOI: 10.1016/S0040-4039(01)90005-X

(29) Koreeda, M.; Luengo, J. I. The anionic oxy-claisen rearrangement of enolates of .alpha.-allyloxy ketones. A remarkable rate accelerating effect exhibited by the nature of the counterion. *J. Am. Chem. Soc*. **1985**, *107* (19), 5572–5573. DOI: 10.1021/ja00305a066

(30) (a) Drapeau, M. P.; Fabre, I.; Grimaud, L.; Ciofini, I.; Ollevier, T.; Taillefer, M. Transition-Metal-Free α-Arylation of Enolizable Aryl Ketones and Mechanistic Evidence for a Radical Process. *Angew. Chem. Int. Ed*. **2015**, *54* (36), 10587–10591. DOI: 10.1002/anie.201502332; (b) Chen, Y.-y.; Zhang, N.-n.; Ye, L.-m.; Chen, J.-h.; Sun, X.; Zhang, Z.-j.; Yan, M. KOt-Bu/DMF promoted intramolecular cyclization of 1,1′-biphenyl aldehydes and ketones: an efficient synthesis of phenanthrenes. *RSC Adv*. **2015**, *5*, 48046–48049. DOI: 10.1039/c5ra07188g; (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. DOI: 10.1021/jacs.6b03282

(31) Jiang, X.; Zeng, Z.; Hua, Y.; Xu, B.; Shen, Y.; Xiong, J.; Qiu, H.; 31Wu, Y.; Hu, T.; Zhang, Y. Merging C–H Vinylation with Switchable 6π-Electrocyclizations for Divergent Heterocycle Synthesis. *J. Am. Chem. Soc*. **2020**, *142* (36), 15585–15594. DOI: 10.1021/jacs.0c07680

(32) Dongbang, S.; Confair, D. N.; Ellman, J. A. Rhodium-Catalyzed C–H Alkenylation/Electrocylization Cascade Provides Dihydropyridines That Serve as Versatile Intermediates to Diverse Nitrogen Heterocycles. *Acc. Chem. Res.* **2021**, *54* (7), 1766–1778. DOI: 10.1021/acs.accounts.1c00027

(33) Cadot, C.; Dalko, P. I.; Cossy, J.; Ollivier, C.; Chuard, R.; Renaud, P. Free-Radical Hydroxylation Reactions of Alkylboronates. *J. Org. Chem*. **2002**, *67* (21), 7193–7202. DOI: 10.1021/jo0201833

(34) (a) Guimond, N.; Gouliaras, C.; Fagnou, K. Rhodium(III)-Catalyzed Isoquinolone Synthesis: The N–O Bond as a Handle for C–N Bond Formation and Catalyst Turnover. *J. Am. Chem. Soc*. **2010**, *132* (20), 6908–6909. DOI: 10.1021/ja102571b; (b) Hyster, T. K.; Rovis, T. Rhodium-Catalyzed Oxidative Cycloaddition of Benzamides and Alkynes via C–H/N–H Activation. *J. Am. Chem. Soc*. **2010**, *132* (30), 10565–10569. DOI: 10.1021/ja103776u

(35) Niu, B.; Liu, R.; Wei, Y.; Shi, M. Catalyst-controlled synthesis of 4-amino-isoquinolin-1(2H)-one and oxazole derivatives. *Org. Chem. Front*. **2018**, *5*, 1466–1470. DOI: 10.1039/c8qo00125a

(36) Yin, Y.; Xing, H.; Ye, J. Efficacy of berberine in patients with type 2 diabetes mellitus. *Metab. Clin. Exp.* **2008**, *57*, 712–717. DOI: 10.1016/j.metabol.2008.01.013

(37) (a) Singh, I. P.; Mahajan, S. Berberine and its derivatives: a patent review (2009 - 2012). *Expert Opin. Ther. Pat.* **2013**, *23*, 215–231. DOI: 10.1517/13543776.2013.746314; b) Lowery, R.; Wilson, J.; Wells, S.; LaCore, T. Administration of Berberine Metabolites. Patent No. US 10,278,961 B2, May 7, 2019

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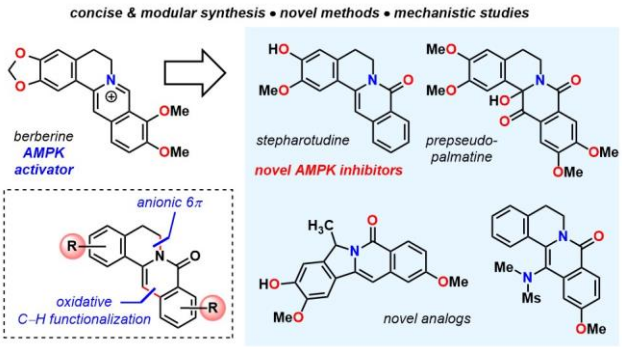

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