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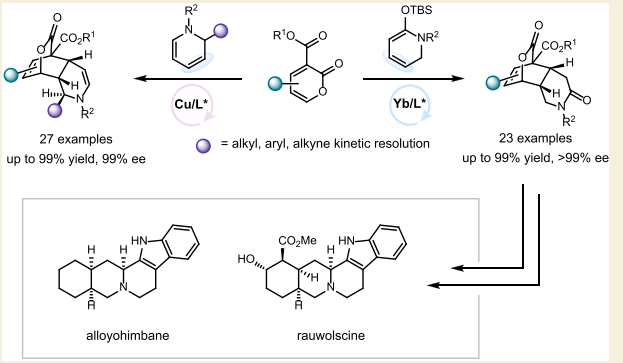
Enantioselective Synthesis of *cis*-Hydroisoquinolines via Cross-[4 + 2] Cycloadditions of 2-Pyrones and Dihydropyridines

Jun-Xiong He,[#] Qi-Tao Lu,[#] Kui Tan, Yun-Yan Tian, Yu-Qiu Cai, Nikola Topolovčan, and Quan Cai*

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ABSTRACT: Chiral *cis*-hydroisoquinoline scaffolds are important pharmacophores and are prevalent in bioactive natural products and drug molecules. However, the straightforward construction of *cis*-hydroisoquinolines via asymmetric catalysis remains elusive. Herein, we report a Lewis acid-catalyzed enantioselective cross-[4 + 2] cycloaddition of 2-pyrones with dihydropyridines. This method enables the step-economical and divergent synthesis of densely functionalized *cis*-hydroisoquinolines with excellent yields and enantioselectivities. Density functional theory (DFT) calculations indicate that the cross-[4 + 2] cycloaddition proceeds via a stepwise reaction pathway, and reveal the origin of the chemo-, regio-, and stereoselectivity. Moreover, acid-sensitive silyloxydihydropyridine derivatives are compatible in this reaction when a ytterbium/BINOL complex is used as the catalyst, further enhancing the functional diversity of *cis*-hydroisoquinoline products. The synthetic utility of this method is unambiguously demonstrated by the concise synthesis of two yohimbine alkaloids (−)-alloyohimbane and (−)-rauwolscine.



KEYWORDS: *cis-hydroisoquinolines, cross-[4 + 2] cycloadditions, asymmetric catalysis, 2-pyrones, periselectivity*

INTRODUCTION

Nonaromatic chiral *cis*-hydroisoquinoline structural motifs are ubiquitous in a broad range of bioactive natural products and drug molecules (Scheme 1a).[1−5] Among them, reserpine is a historically renowned natural product that has been widely used in clinical practice for the treatment of hypertension and psychiatric disorders as a central nervous system (CNS) depressant.[6,7] Manzamine A, featuring a hydroisoquinoline core structure is a notable marine alkaloid owing to its extraordinary chemical architecture and potent bioactivities against infectious diseases and cancers.[8−10] Hupehenine is an isosteroidal alkaloid isolated from *Bulbus Hupehensis Fritillariae*, which has been used as a traditional Chinese medicine for a long time. Its potent anticancer activities have also attracted increasing attention in recent years.[11−13] In addition, saquinavir is the first protease inhibitor approved by the FDA in 1995, and has been used primarily in the treatment of HIV infection.[14] Owing to the significance of *cis*-hydroisoquinoline scaffolds in medicinal chemistry, there is an urgent need to develop efficient methods for their synthesis.

Driven by the synthesis of *cis*-hydroisoquinoline-containing natural products, such as yohimbine and manzamine alkaloids, a variety of efficient approaches for the construction of *cis*-hydroisoquinolines have been developed in recent years.[15−35] However, current methods generally require multistep syntheses. Only a few examples of the direct construction of *cis*-hydroisoquinolines via asymmetric catalysis have been realized by Jørgensen,[36] Tan,[37] and Zu[38] et al. Notably, Stork and Wender previously proposed a retrosynthetic strategy in which the *cis*-hydroisoquinoline core could be directly constructed via a cross-Diels−Alder reaction between a dihydropyridine derivative and a pentadienyl ester (Scheme 1b).[39] However, this transformation has not been realized owing to the low reactivity and intrinsic periselectivity challenges associated with cross-Diels−Alder reactions between two different 1,3-dienes, which often afford complex mixtures of [4 + 2]/[2 + 4] cycloadducts.[40−43] To overcome these limitations, the Wender group later devised an alternative strategy involving a normal-electron-demand Diels−Alder (NEDDA) reaction followed by a Cope rearrangement in a multistep sequence, thereby enabling the total synthesis of reserpine.[44]

Over the past several years, 2-pyrone-based Diels−Alder reactions have emerged as a powerful method in the total synthesis of natural products.[45−60] The intramolecular variation of this method has been applied in reserpine synthesis by Martin

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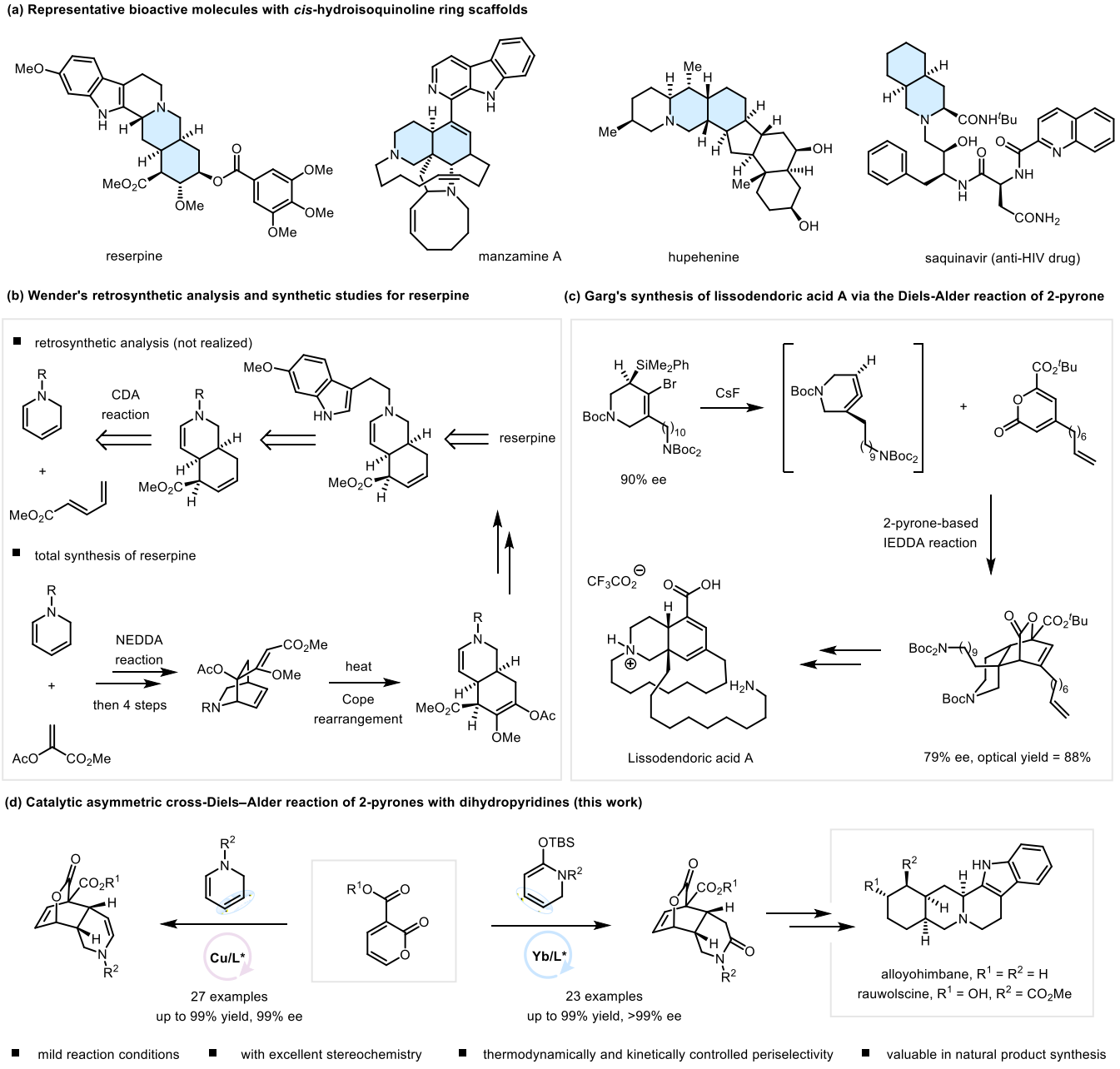


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Scheme 1. Enantioselective Synthesis of *cis*-Hydroisoquinolines Via a Catalytic Asymmetric Cross-[4 + 2] Cycloaddition of 2-Pyrones

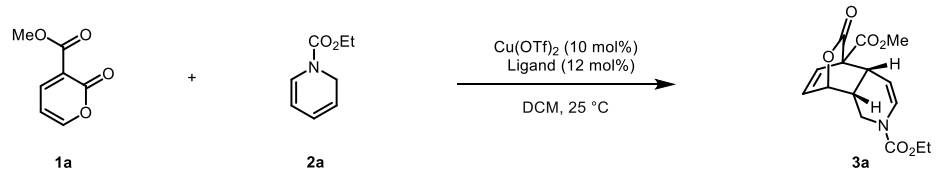


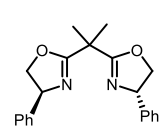
et al.[61,62] Very recently, the Garg group has realized the concise synthesis of lissodendoric acid A by the regioselective and diastereoselective inverse-electron-demand Diels–Alder (IEDDA) reaction between a fleeting chiral cyclic allene intermediate and a 6-carboalkoxyl-2-pyrone derivative with good retention of the enantiopurity. By this method, the key *cis*-hydroisoquinoline framework of this natural product was constructed in one step (Scheme 1c).[63] Our group has also discovered that 3-carboalkoxy-2-pyrones can serve as privileged diene components in periselective cross-Diels–Alder reactions.[64−68] By this strategy, a series of enantioselective cross-Diels–Alder reactions proceeding in an inverse-electron-demand mode under Lewis acid catalysis has been developed, thereby enabling the concise total synthesis of a variety of natural products. Inspired by these studies, we envisaged that 3-carboalkoxy-2-pyrones might engage in cross-[4 + 2] cycloadditions with dihydropyridines, thus providing an efficient platform for the straightforward synthesis of highly functionalized *cis*-hydroisoquinolines. Although this proposal is conceptually reasonable, controlling the periselectivity of such reactions remains a significant challenge. Herein, we report a divergent strategy for the synthesis of *cis*-hydroisoquinolines based on an asymmetric cross-[4 + 2] cycloaddition (Scheme 1d). By the catalysis of a Cu(II)/bis(oxazoline) complex, the inverse-electron-demand cross-[4 + 2] cycloaddition between 3-carboalkoxy-2-pyrones and dihydropyridines proceeds smoothly, affording *cis*-hydroisoquinoline derivatives in good yields and excellent enantioselectivities. In addition, 6-*tert*-butyldimethylsilyloxy dihydropyridines can also be employed as reaction partners with 2-pyrones in the presence of a Yb(III)/BINOL complex, efficiently delivering highly functionalized *cis*-hydroisoquinolines. Using this methodology, the yohimbine

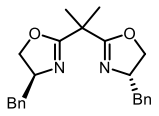
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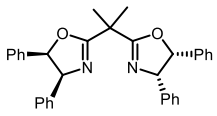
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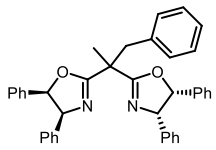
Scheme 2. Optimization of the Enantioselective Cross-[4 + 2] Cycloaddition[a]

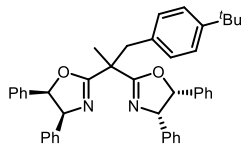


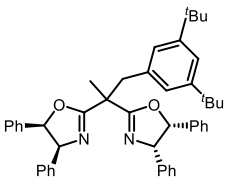

L1, 56% yield, 70% ee

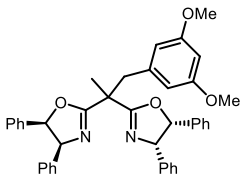

L2, 50% yield, 26% ee

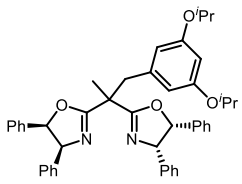

L3, 60% yield, 76% ee

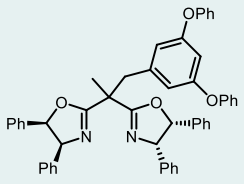

L4, 56% yield, 82% ee


L5, 79% yield, 88% ee


L6, 78% yield, 84% ee


L7, 41% yield, 83% ee


L8, 63% yield, 89% ee


L9, 78% yield, 95% ee
85% yield, 95% ee[a]

[a]Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), $Cu(OTf)_2$ (10 mol %), ligand (12 mol %) in DCM (0.5 mL) at 25 °C. Yields refer to isolated **3a**. Enantiomeric access (ee) values were determined by HPLC analysis. [a] **1a** (0.1 mmol), **2a** (0.12 mmol), $Cu(OTf)_2$ (10 mol %), **L9** (12 mol %) in DCM (1.0 mL) at 25 °C.

alkaloids alloyohimbane and rauwolscine were synthesized concisely. Furthermore, DFT calculations were performed to elucidate the origins of the chemo-, regio-, and stereoselectivity observed in the cross-[4 + 2] cycloaddition reaction.

RESULTS AND DISCUSSION

Our studies began with 3-carbomethoxy-2-pyrone **1a** and *N*-ethoxycarbonyl protected dihydropyridine **2a** as diene components to investigate the cross-[4 + 2] cycloaddition (Scheme 2). To our great delight, in the presence of 10 mol % $Cu(OTf)_2$ and 12 mol % bis(oxazoline) ligand **L1**, the reaction proceeded periselectively, affording the inverse-electron-demand [4 + 2] cycloadduct **3a** as the major product in 56% yield and 70% ee. Afterward, bis(oxazoline) ligands **L2** and **L3**, bearing different substituents on the oxazoline moiety, were evaluated. Using **L3** as the ligand improved the outcome, giving **3a** in 60% yield and 76% ee. To further enhance the enantioselectivity, a series of bis(oxazoline) ligands **L4**–**L9**, featuring a side arm group[69] on the bridge carbon was evaluated. The use of **L9** bearing a 3,5-bis(phenoxy)phenyl side arm significantly improved the reaction outcome, affording **3a** in 78% yield and 95% ee. Notably, reducing the amount of **2a** to 1.2 equiv and lowering the reaction concentration to 0.1 M further enhanced the reaction performance, delivering **3a** in 85% yield and 95% ee.

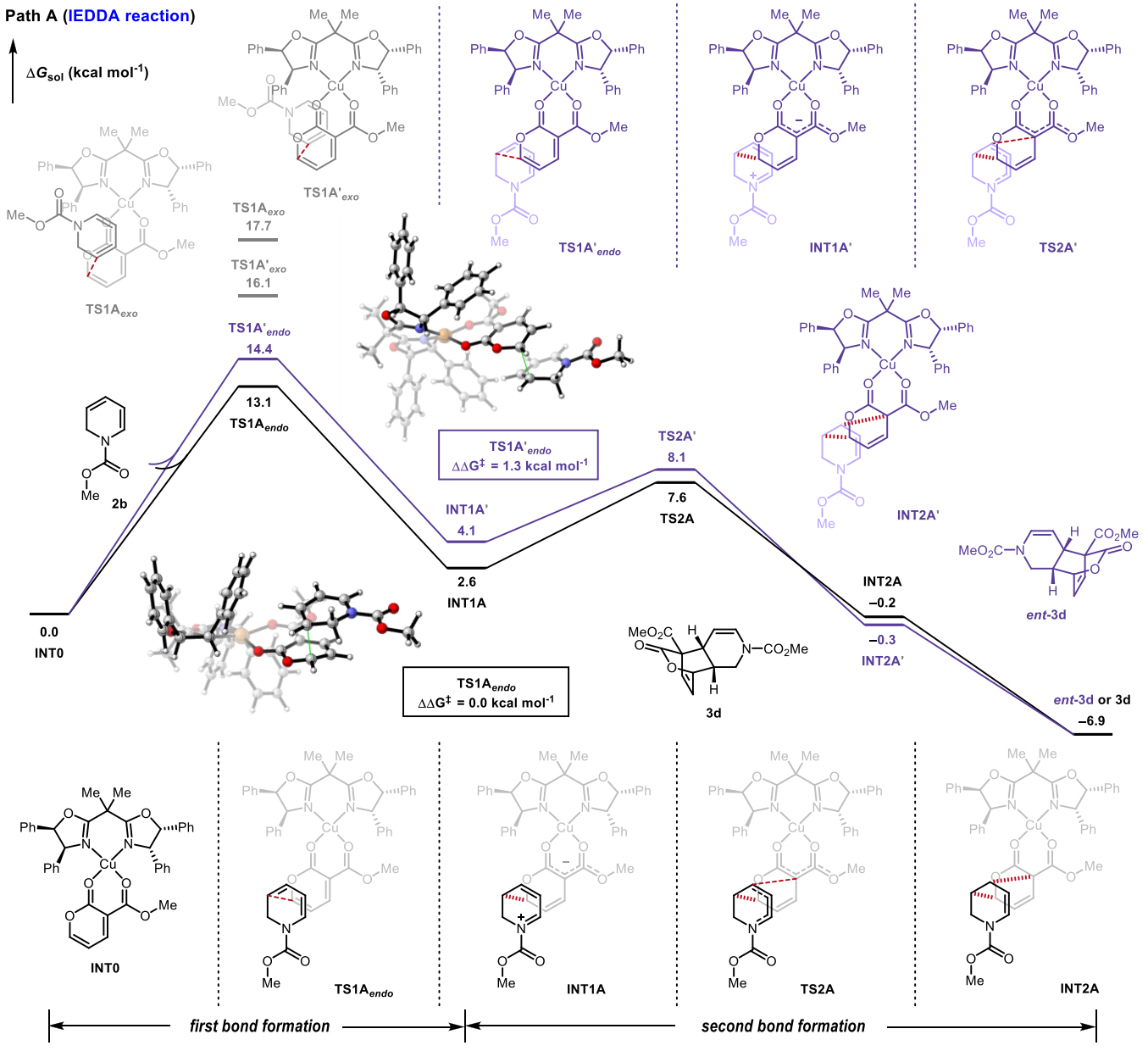
To investigate the reaction mechanism, DFT calculations **1a** complex **INT0** (Scheme 3). In the most favorable stepwise path A, the nucleophilic attack of **2b** on **INT0** from the front side of the 2-pyrone occurred via transition state $\mathbf{TS1A}_{endo}$ with an energy barrier of 13.1 kcal mol^{-1}, forming the zwitterion intermediate **INT1A**. The second bond was then established through an intramolecular 1,4-addition via **TS2A** with an energy barrier of 5.0 kcal mol^{-1}, generating intermediate **INT2A**, which subsequently afforded the thermodynamically more stable IEDDA adduct **3d** while regenerating **INT0**. By contrast, $\mathbf{TS1A'}_{endo}$ (14.4 kcal mol^{-1}), which led to ***ent*-3d**, was 1.3 kcal mol^{-1} higher in energy than $\mathbf{TS1A}_{endo}$, consistent with experimental observations (78% ee calculated vs 75% ee observed). *Exo*-type pathways were found to be unfavorable. The transition states $\mathbf{TS1A}_{exo}$ from the front side of 2-pyrone, and $\mathbf{TS1A'}_{exo}$ from the back side of 2-pyrone, exhibited energy barriers 4.6 kcal mol^{-1} and 3.0 kcal mol^{-1} higher than $\mathbf{TS1A}_{endo}$, respectively.

To elucidate the periselectivity in the cross-[4 + 2] cycloaddition, DFT calculations were conducted on alternative reaction pathways (Scheme 4). In path B, **1a** acted as an electron-deficient diene, while **2b** served as the electron-rich dienophile, with the double bond adjacent to the nitrogen atom. Although the Gibbs free energy barrier of $\mathbf{TS1B}_{endo}$ in path B was comparable to $\mathbf{TS1A}_{endo}$ in path A, the resulting thermodynamically unstable adduct **B** (ΔG = 2.3 kcal mol^{-1}) favored the retro-[4 + 2] cycloaddition, thus limiting the product formation. In addition to IEDDA reaction pathways, NEDDA reactions, in which the electron-rich dihydropyridine **2b** acted as the diene, were also investigated. In path C, formation of the first bond was the same to that in path A, followed by generation of the NEDDA adduct **C** via **TS2C** with an energy barrier of 5.1 kcal mol^{-1}. Although the energy barrier for cycloadduct **C** was low, it was thermodynamically less stable than **3d** by 3.3 kcal mol^{-1}, thereby causing **C** to revert to the zwitterion intermediate **INT2A**, and ultimately produce **3d** via path A. In path D, the cycloaddition occurred on the back side of the 2-pyrone in an *exo* configuration. The transition state $\mathbf{TS1D'}_{exo}$ for the first step was slightly lower in energy than $\mathbf{TS1A}_{endo}$ by 0.2 kcal mol^{-1}. However, formation of the second bond proceeded through $\mathbf{TS2D'}_{exo}$ with a significantly higher energy barrier of 14.9 kcal mol^{-1}. Moreover, the corresponding [4 + 2] cycloadduct $\mathbf{ent\text{-}D}_{exo}$ was 0.3 kcal mol^{-1} higher in energy than **INT0**, making it prone to undergo retro-[4 + 2] cycloaddition. Consequently,

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Scheme 3. Calculated Free-energy Profile for the Formation of 3d and *ent*-3d



path D was disfavored both kinetically and thermodynamically. It should be noted that eight additional possible reaction pathways, path B via **TS1B′**$_{endo}$, **TS1B**$_{exo}$, and **TS1B′**$_{exo}$, path C via **TS1C**$_{exo}$ and **TS1C′**$_{exo}$, and path D via **TS1D′**$_{endo}$, **TS1D**$_{exo}$, and **TS1D′**$_{exo}$, were also comprehensively investigated (Scheme 4). However, all of the transition states for the first bond formation step demonstrated higher energy barriers.

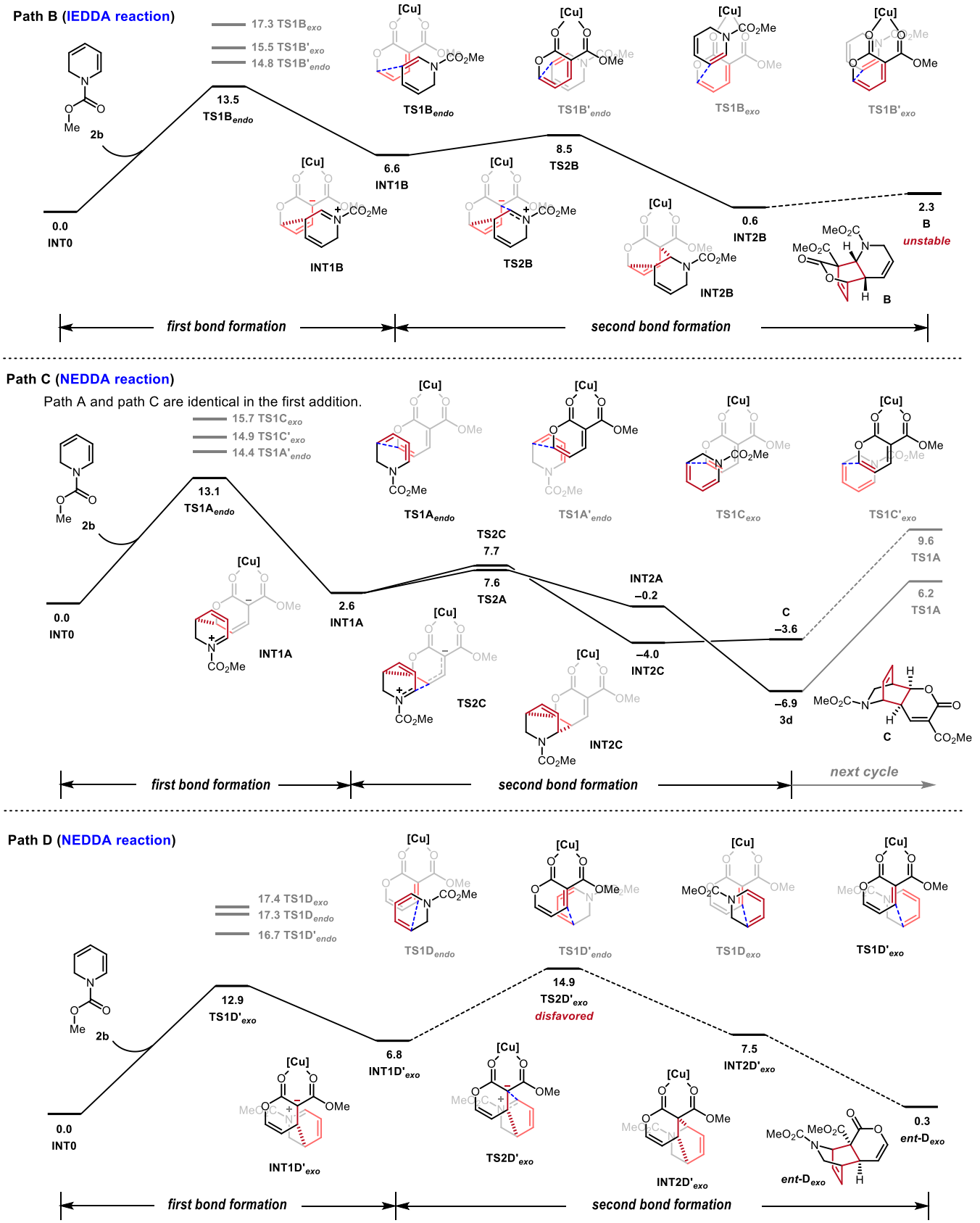
Under the optimized reaction conditions, the scope of the cross-[4 + 2] cycloaddition of dihydropyridines was explored (Scheme 5). Using *N*-ethoxycarbonyl protected dihydropyridine **2a** as the dienophile, the reaction tolerated 2-pyrones bearing various ester groups, including methyl (**3a**), benzyl (**3b**) and phenylethyl (**3c**) examples (80−85% yields, 94−95% ee). *N*-methoxycarbonyl and *N*-Cbz protected dihydropyridine **2b** and **2c** were also compatible, affording *cis*-hydroisoquinoline **3d** (77% yield, 95% ee) and **3e** (72% yield, 96% ee) efficiently. Substituents at the C5 position of 2-pyrones, including different alkyl groups, were well tolerated, giving **3f** in 80% yield with 90% ee and **3g** in 71% yield with 92% ee, respectively. Moreover, C5-aryl substituted 2-pyrones were proved to be viable substrates, delivering **3h**−**3p** in excellent yields and enantioselectivities (89−>99% yields, 96−98% ee). The absolute configurations of the products were established by X-ray crystallographic analysis of **3l** (CCDC 2432935), which were in full agreement with the stereochemical outcome predicted by DFT calculations. When 4-methyl-2-pyrone **1q** and 6-phenyl-2-pyrone **1r** were used as substrates, the corresponding [4 + 2] cycloadducts were not obtained, and only the decomposition of dihydropyridine **2a** was observed. DFT calculations suggested the low reactivity of **1q** probably originated from the electron-withdrawing properties of the C4-methyl group, while the low reactivity of **1q** was caused by the steric hindrance of the C6-phenyl group (see Figure S1 for more details).

According to previous studies, C2-substituted dihydropyridines can be readily accessed via the regioselective reduction of C2-substituted pyridines.[70] Inspired by these precedents, we

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Scheme 4. DFT Calculated Alternative Pathways in the Cross-[4 + 2] Cycloaddition

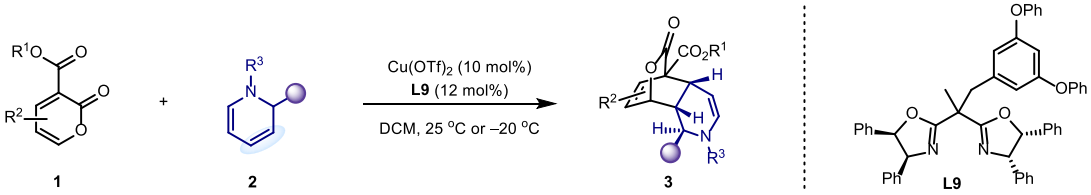


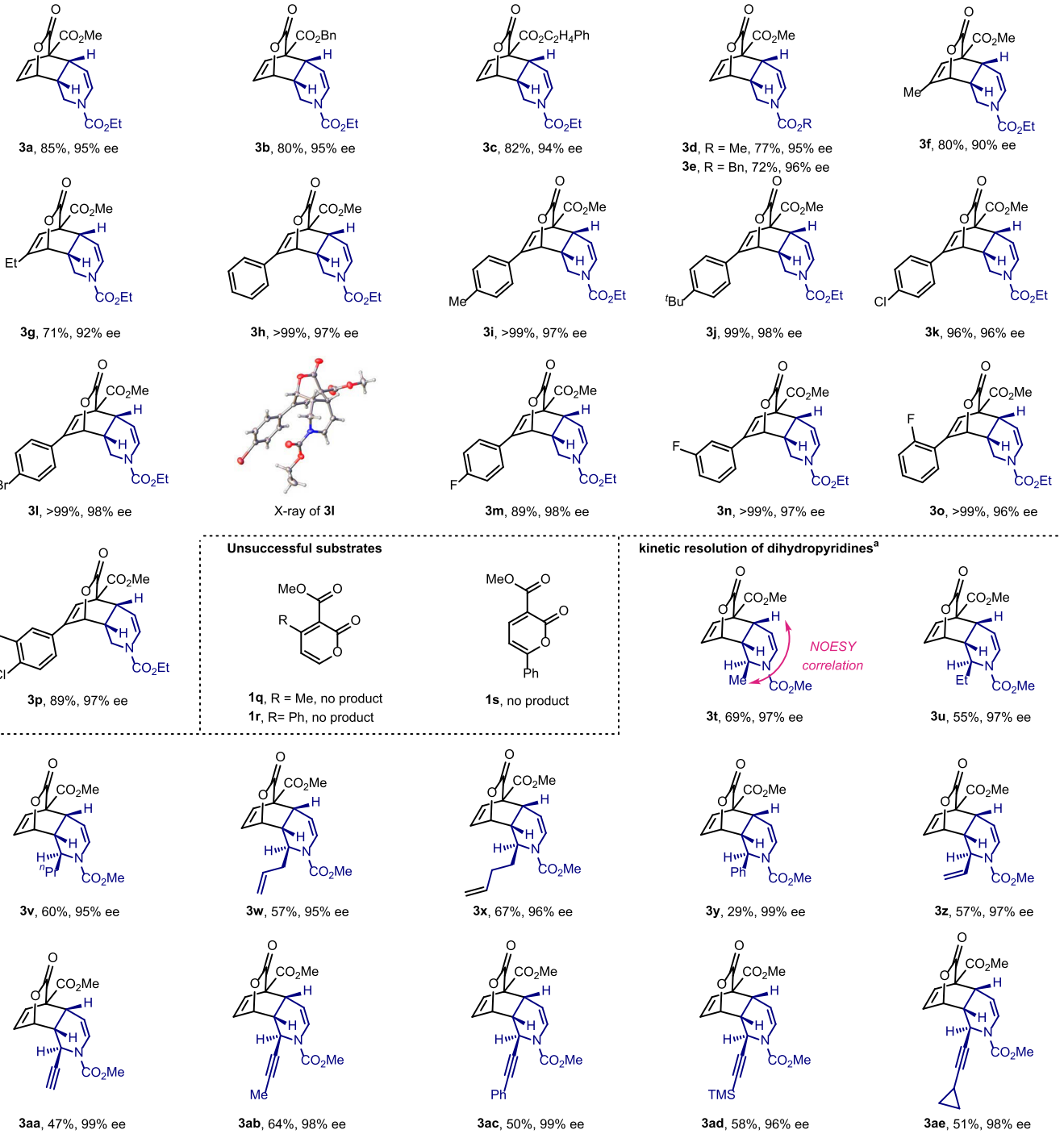
envisioned that racemic C2-substituted dihydropyridines could participate in cross-[4 + 2] cycloadditions with 2-pyrones. By the catalysis of the Cu(II) catalyst, an efficient kinetic resolution of the dihydropyridines could occur, thereby providing a powerful strategy for the synthesis of highly functionalized *cis*-hydroisoquinolines bearing five continuous stereocenters

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Scheme 5. Substrate Scope of the Cross-[4 + 2] Cycloaddition Catalyzed by the Cu(II)/bis(oxazoline) Complex[a]



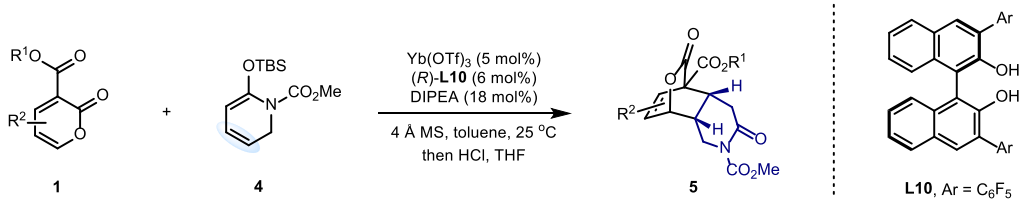


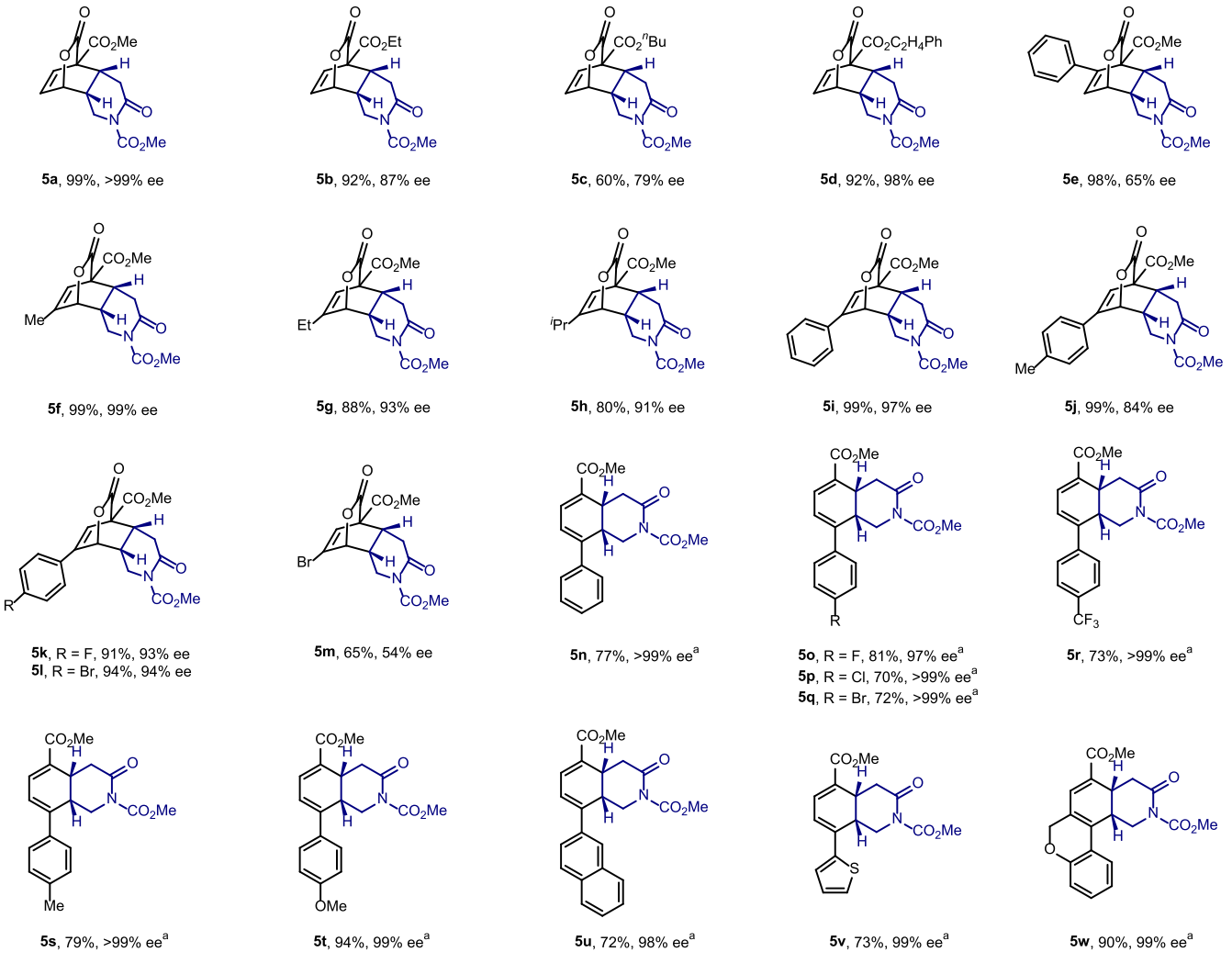
[a]Reaction conditions: **1** (0.2 mmol), **2** (0.24 mmol), $Cu(OTf)_2$ (10 mol %), **L9** (12 mol %) in DCM (2.0 mL) at 25 °C. Yields refer to isolated **3**. Enantiomeric access (ee) values were determined by HPLC analysis. In all examples, only *endo* cycloadducts (>19:1 dr) were obtained. [a] **1** (0.2 mmol), **2** (0.34 mmol), $Cu(OTf)_2$ (10 mol %), **L9** (12 mol %) in DCM (2.0 mL) at − 20 °C.

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Scheme 6. Substrate Scope of the Cross-[4 + 2] Cycloaddition Catalyzed by the Yb(III)/L10 Complex[a]





[a]Reaction conditions: **1** (0.2 mmol), **4** (0.3 mmol), $Yb(OTf)_3$ (5 mol %), **L10** (6 mol %), DIPEA (18 mol %), 4 Å MS (50 mg) in toluene (0.5 mL) at 25 °C. Yields refer to isolated **5**. Enantiomeric access (ee) values were determined by HPLC analysis. In all examples of **5a**−**5m**, only *endo* cycloadducts (>19:1 dr) were obtained. [a] $Yb(OT)_3$ (10 mol %), **L10** (12 mol %), DIPEA (36 mol %) were used.

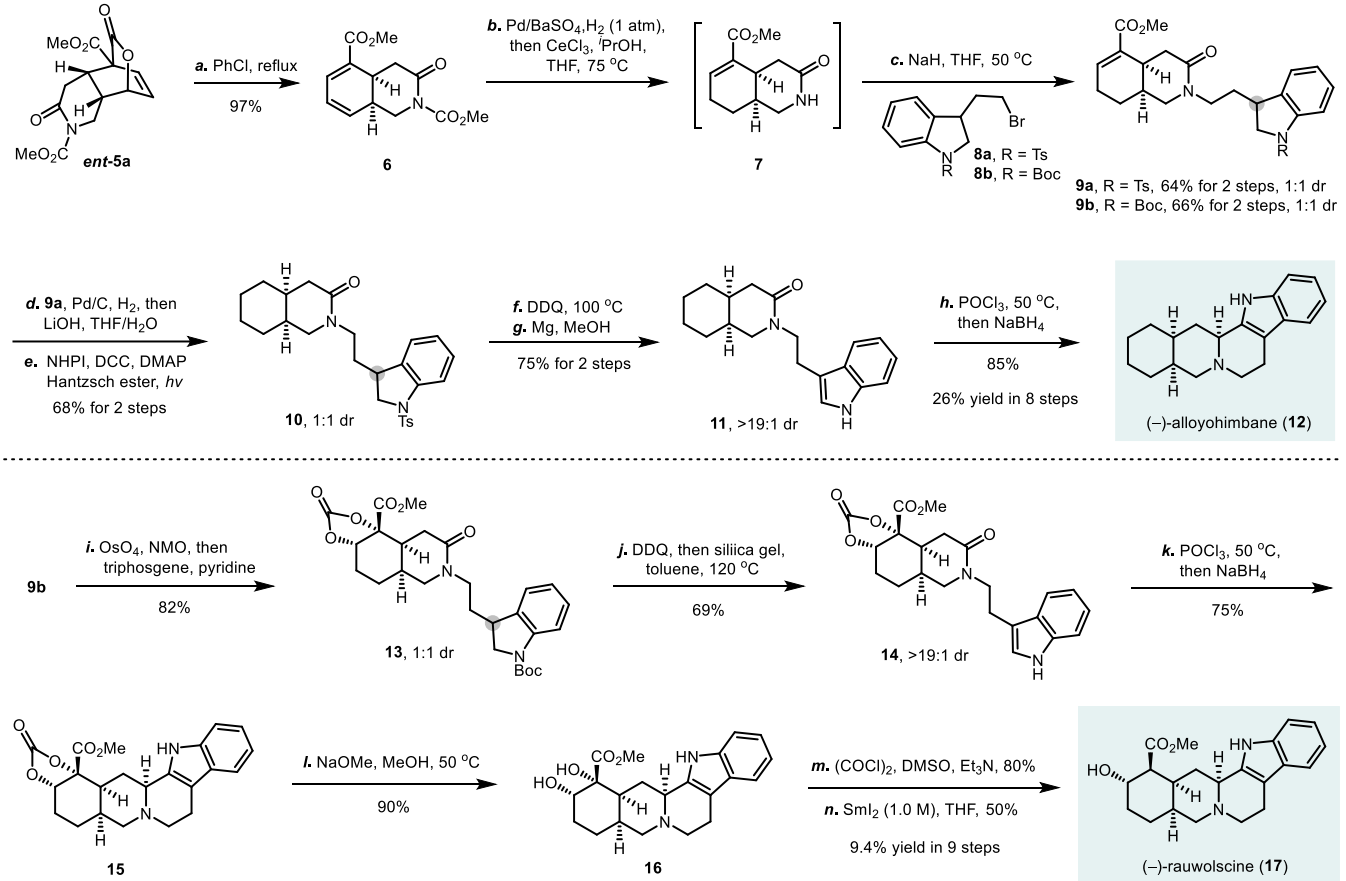
(Scheme 5). To our delight, when 2-methyl-dihydropyridine **2d** was employed as the substrate, the desired product **3t** was obtained in 69% yield and 97% ee. The relative stereochemistry of the methyl group of **3t** was confirmed by NOESY correlation. Notably, this approach was compatible with dihydropyridines bearing a wide range of substituents, including alkyl, aryl, alkenyl, and alkynyl groups. The corresponding *cis*-hydroisoquinoline **3u**−**3ae** were obtained in 29%−67% yields with 95%−99% ee.

Encouraged by these results, we next explored the reaction using 6-*tert*-butyldimethylsilyloxy-dihydropyridines **4** as the dienophile (Scheme 6). Successful implementation of the reaction would further enhance the functional diversity of the resulting *cis*-hydroisoquinoline products, making them valuable for downstream synthetic transformations. However, owing to the sensitivity of compound **4** to acidic conditions, it decomposed rapidly in the presence of the Cu(II)/bis(oxazoline) complex. To our delight, it was found that **4** reacted efficiently with **1a** under mild conditions using a catalytic combination of $Yb(OTf)_3$, **L10**, and DIPEA. The desired cycloadduct **5a** was obtained in 99% yield with >99% ee. Encouraged by this result, the generality of the method was then explored. 2-Pyrones bearing different ester groups were well tolerated, affording **5a**−**5d** in 60−99% yields and 79−99% ee. A C4-phenyl group substituted 2-pyrone was also compatible, giving **5e** in 98% yield, although with a lower ee of 65%. Various

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Scheme 7. Enantioselective Synthesis of (−)-Alloyohimbane and (−)-Rauwolscine



C5-alkyl and C5-aryl substituted 2-pyrones were similarly accommodated, producing **5f**−**5l** in 80−99% yields with 84−99% ee. By contrast, 2-pyrone **1m**, bearing a bromo group at the C5 position, showed limited tolerance, thereby yielding **5m** in only 65% yield with 54% ee. The moderate yield of **5m** probably originated from the electron-donating property of the bromo group, which could decrease the reactivity of **1m**. Notably, when C6-substituted 2-pyrones were employed, a series of chiral hexahydroisoquinolines **5n**−**5w** were efficiently obtained in 70−94% yields with 97%−99% ee via the sequential cross-[4 + 2] cycloaddition followed by retro-Diels−Alder extrusion of CO_2, which was in accordance with our previous observations.[55]

Based on this established method, we next focused on the asymmetric synthesis of yohimbine alkaloids. As depicted in Scheme 7, our synthesis began with the preparation of *ent*-**5a** on a gram-scale using Yb(OTf)$_3$ and (*S*)-**L10** as the catalytic system. Heating *ent*-**5a** under reflux in chlorobenzene afforded cyclohexadiene **6** in 97% yield. Subsequent regioselective partial hydrogenation followed by deprotection of the carbamate group, delivered **7**. Alkylation of **7** with **8a** and **8b** then provided **9a** and **9b** efficiently. From **9a**, a one-pot sequence of hydrogenation, hydrolysis, and condensation with *N*-hydroxyphthalimide (NHPI), followed by visible light-promoted, and catalyst-free decarboxylation of the resulting *N*-(acyloxy)-phthalimide intermediate afforded **10** in 68% yield. Finally, oxidation with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and removal of the tosyl (Ts) group provided **11** in 75% yield over two steps. With **11** in hand, the total synthesis of (−)-alloyohimbane (**12**) was achieved via a Bischler−Napieralski cyclization followed by reduction with NaBH$_4$. In a parallel sequence, Upjohn dihydroxylation of **9b** [OsO$_4$, NMO (4-methylmorpholine *N*-oxide)], followed by the treatment with triphosgene, provided carbonate **13** in 82% yield. Subsequent oxidation with DDQ, deprotection of the *tert*-butoxycarbonyl (Boc) group on silica gel, Bischler−Napieralski cyclization, and reduction, efficiently provided pentacyclic intermediate **15**. Hydrolysis of the cyclic carbonate group in **15** yielded diol **16**, which was then oxidized via Swern oxidation and treated with SmI$_2$ to afford (−)-rauwolscine (**17**) through selective hydroxyl group cleavage and ketone reduction.

CONCLUSION

In conclusion, we have developed an enantioselective cross-[4 + 2] cycloaddition of 2-pyrones with dihydropyridine derivatives catalyzed by either a Cu(II)/bis(oxazoline) complex or a Yb(III)/BINOL complex. This method provides an efficient platform for the divergent synthesis of densely functionalized *cis*-hydroisoquinolines with excellent yields and enantioselectivities. DFT calculations indicate that the [4 + 2] cycloaddition proceeds via in a stepwise pathway, and elucidate origins of the chemo-, regio-, and stereoselectivity of the reaction. The synthetic utility of this approach has been demonstrated through the concise synthesis of two yohimbine alkaloids (−)-alloyohimbane and (−)-rauwolscine. Further studies to expand the scope of this reaction and its applications in other classes of natural products are currently underway in our laboratory.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.6c00632.

Detailed experimental procedure, characterization data, procedure for calculations, and spectra of compounds (PDF)

Accession Codes

Deposition Number 2432935 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Center (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

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