JACS Au
AN OPEN ACCESS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Article

Regio- and Enantioselective Hydromethylation of 3-Pyrrolines and Glycals Enabled by Cobalt Catalysis

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Cite This: *JACS Au* 2024, 4, 2312−2322
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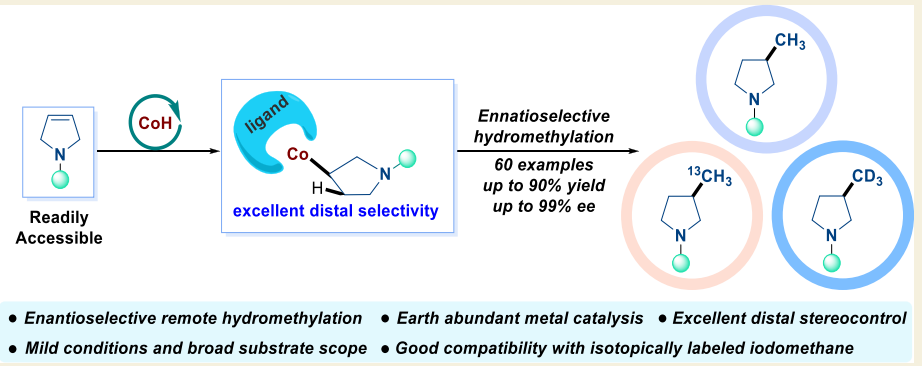


ABSTRACT: Enantioenriched 3-methylpyrrolidine, with its unique chiral nitrogen-containing core skeleton, exists widely in various functional molecules, including natural products, bioactive compounds, and pharmaceuticals. Traditional methods for synthesizing these valuable methyl-substituted heterocycles often involve enzymatic processes or complex procedures with chiral auxiliaries, limiting the substrate scope and efficiency. Efficient catalytic methylation, especially in an enantioselective manner, has been a long-standing challenge in chemical synthesis. Herein, we present a novel approach for the remote and stereoselective installation of a methyl group onto N-heterocycles, leveraging a CoH-catalyzed asymmetric hydromethylation strategy. By effectively combining a commercial cobalt precursor with a modified bisoxazoline (BOX) ligand, a variety of easily accessible 3-pyrrolines can be converted to valuable enantiopure 3-(isotopic labeling)methylpyrrolidine compounds with outstanding enantioselectivity. This efficient protocol streamlines the two-step synthesis of enantioenriched 3-methylpyrrolidine, which previously required up to five or six steps under harsh conditions or expensive starting materials.

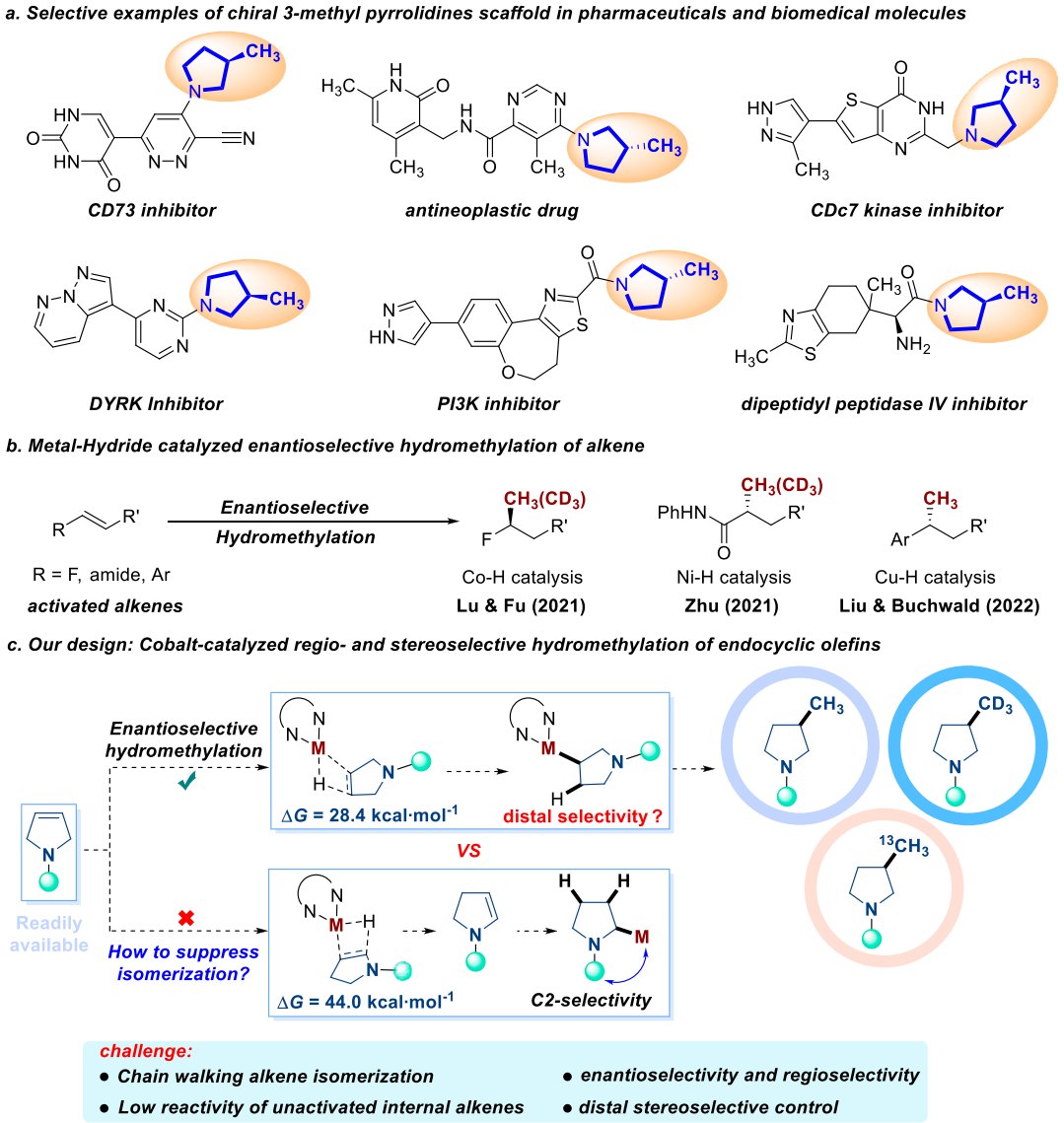
KEYWORDS: *asymmetric hydromethylation, cobalt catalysis, distal stereocontrol, desymmetrization, enantioenriched 3-methylpyrrolidine*

INTRODUCTION

Enantioenriched 3-methylpyrrolidine derivatives are of significant importance in both natural products and pharmaceutical molecules, often serving as essential synthetic intermediates for the production of drug candidates (Scheme 1a).[1−5] The strategic introduction of methyl substituents into N-heterocyclic cores offers a powerful means to finely tune the conformational preferences of molecules, thereby enabling precise adjustments to their 3D structures.[6,7] This ability to modulate molecular shape can lead to substantial enhancements in terms of potency, efficacy, and stability while keeping changes in molecular weight minimal.[8−10] Given the pivotal role that methyl groups play in chiral organic compounds, the direct and enantioselective installation of methyl groups onto molecules, especially within heterocyclic cores, has garnered significant attention. However, only limited methodologies have been developed to construct the chiral 3-methylpyrrolidine compound, including zymochemistry-based approaches[11] and chiral pool conversions.[12−14] These synthetic strategies often necessitate intricately designed starting materials and involve multistep; complex reaction sequences conducted under harsh conditions. This results in relatively low overall yields, limited substrate scope, poor atom and step economy, and challenges in achieving precise enantioselectivity control. Additionally, the incorporation of isotopic methyl groups into drug molecules is of significant interest in physiological investigation and medical research but poses a formidable challenge in synthetic chemistry.[15−18] Given the significance of enantiopure 3-(isotopic labeling)methyl pyrrolidine com-

Received: March 27, 2024
Revised: May 25, 2024
Accepted: May 29, 2024
Published: June 11, 2024

Scheme 1. Strategies for Hydromethylation of Alkenes



pounds, there is a pressing need for the development of an exceptionally efficient synthetic protocol that facilitates the construction of these valuable structural motifs using readily available raw materials. Such a method would be highly desirable and hold great promise for advancing the synthesis of complex molecules with enhanced precision and utility in various scientific and industrial applications.

Transition metal-catalyzed hydrofunctionalization of unsaturated olefins has been rapidly developed in recent years.[19−63] It provides a direct and efficient method for the formation of $C(sp^3)-C(sp^3)$ with stereocenters by introducing hydrogen and functional groups on unsaturated double bonds,[64−82] which employs stable and abundant alkenes as pronucleophiles instead of the moisture- and air-sensitive organometallic reagents typically required in traditional cross-coupling.[83−88] Inspired by these achievements and considering the importance of enantioenriched 3-methylpyrrolidine derivatives, we wondered whether a direct enantioselective installation of a methyl group on readily available 3-pyrrolines through low-valent CoH catalysis can be achieved. As is well-known, methyl is the smallest alkyl substituent. In the process of introducing methyl group on a molecule, the regulation of stereoselectivity is still a major difficulty and challenge in organic synthesis.[57,89−99] Up to now, transition metal-catalyzed enantioselective hydromethylation reactions have made limited progress. In 2021, Lu and Fu's research group achieved a significant breakthrough in the field of cobalt-catalyzed hydroalkylation reactions, enabling the highly efficient synthesis of chiral methylated fluoroalkanes from fluorinated olefins.[100] In the same year, Zhu and Zhou have developed a nickel-catalyzed asymmetric hydromethylation to successfully construct methyl-substituted chiral amides in good efficiency.[101] Subsequently, Liu and Buchwald et al. developed a CuH-catalyzed asymmetric olefins hydromethylation protocol, enabling the enantioselective installation of a methyl group onto a small molecule via the involvement of in situ generated MeI and the pronounced iodide effect[102] (Scheme 1b). Although some achievements have been made in the asymmetric hydromethylation, the alkenes used in this strategy are usually limited to activated acyclic alkenes,[103] such as fluorinated, arylated olefins or substituted acrylamides, and

https://doi.org/10.1021/jacsau.4c00275
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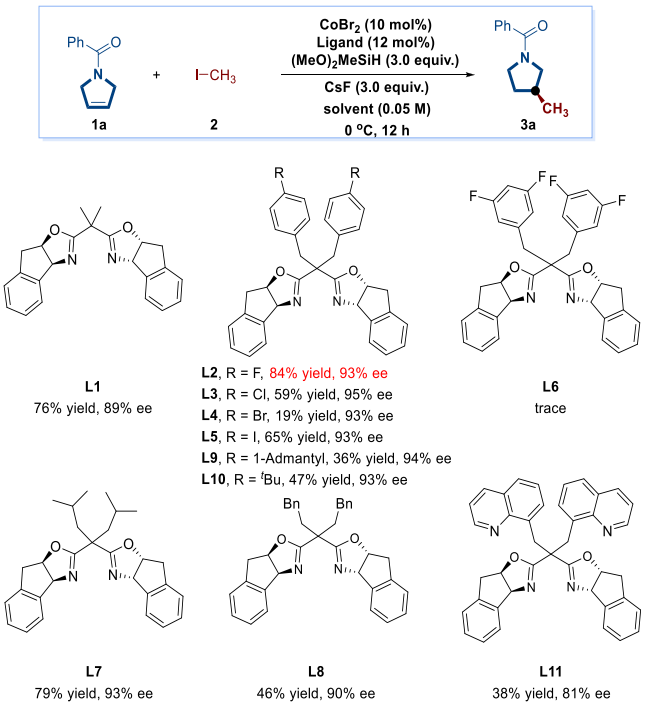
achieving the enantioselective regulation of hydromethylation of unactivated endocyclic olefins remains a challenge.

Herein, we disclose the direct installation of a methyl group onto a N-heterocyclic molecule via regio- and stereoselective hydromethylation of 3-pyrrolines enabled by CoH catalysis. Despite our prior success in achieving asymmetric C(sp^3)−C(sp^3) coupling,[78] the precise stereoselective control of methyl groups remain a formidable challenge, primarily due to the minimal size and inherent radical reactivity of methyl groups. Additionally, the transition metal alkyl intermediate formed during the reaction is prone to β-H elimination, resulting in olefin isomerization byproducts through double bond chain walking in the heterocycle (Scheme 1c). To overcome these challenges, it is crucial to accelerate the rate of combination of transition metal alkyl species with methyl radicals, surpassing the rate of β-H elimination of the transition metal alkyl intermediate. In this context, the choice of the transition metal is paramount. Cobalt, being one of the most promising earth-abundant transition metals, has been successfully employed in catalytic alkene hydrofunctionalization reactions owing to its unique characteristics and prominent catalytic properties.[22,27,48−50,53,57,104−109] In this work, we utilized unsaturated nitrogen heterocyclic olefins with a weak directing group as substrates, and the reaction was catalyzed by a system based on cobalt catalysts and chiral bisoxazoline ligands. This strategic approach effectively prevents β-H elimination due to the introduction of a cobalt catalyst. Density functional theory (DFT) calculation confirms the difficulty of the formation of olefin isomerization byproduct by chain walking in the presence of cobalt catalyst, favoring direct olefin hydrometallization and leading to the desired C3-methylation products (see more details in the Supporting Information).

RESULTS AND DISCUSSION

We initially explored the reaction conditions using (2,5-dihydro-1*H*-pyrrol-1-yl)(phenyl)methanone **1a** and iodomethane **2** as model substrates. Given the significance of bisoxazoline chiral ligands derived from the indene skeleton in alkene hydrofunctionalization reactions, we commenced by screening various indene skeleton chiral ligands. The indene skeleton chiral ligand **L1** with a methyl modification led to the formation of the 3-methylated pyrrolidine product in 76% yield with 89% ee. Notably, when a 4-fluorophenyl-modified indene chiral skeleton oxazoline ligand was employed, the yield and enantioselectivity improved significantly, affording product **3a** in 84% yield and 93% ee (Table 1, entry 1). However, the use of ligands **L3**−**L6** with other halogen modifications on the benzene ring resulted in lower yields of target product **3a**. The isopropyl-modified chiral ligand **L7**, while achieving a high ee value of 93%, yielded a slightly lower yield than **L2**. Ligands **L8**−**L11**, modified with benzyl, 4-(1-admantyl)benzyl, 4-*tert*-butylbenzyl and 8-quinolinylmethyl groups, exhibited improved enantioselectivity, albeit with relatively lower yields. Ultimately, we selected 4-fluorophenyl-modified chiral bisoxazoline ligand **L2** as the optimal ligand. We further investigated the impact of other parameters on reaction efficiency. When CoI_2 served as the cobalt source, the ee value remained consistent, but the yield significantly decreased (Table 1, entry 2). Subsequently, different hydrogen sources were tested. While conversion occurred with $(MeO)_3SiH$, $(EtO)_2MeSiH$, and $PhMeSiH_2$ instead of $(MeO)_2MeSiH$, it resulted in slightly lower ee values and substantially reduced yields (Table 1, entry 3−5). Alternative bases were explored to evaluate their impact

Table 1. Conditions Optimization[a]



entry	deviations	yield (%)	ee (%)
1	none	**84**	**93**
2	CoI_2 instead of $CoBr_2$	30	91
3	$(MeO)_3SiH$ instead of $(MeO)_2MeSiH$	24	85
4	$(EtO)_2MeSiH$ instead of $(MeO)_2MeSiH$	40	83
5	$PhMeSiH_2$ instead of $(MeO)_2MeSiH$	18	83
6	KF instead of CsF	48	92
7	K_3PO_4 instead of CsF	NR	
8	Et_2O instead of DME	30	84
9	DCE instead of DME	54	71

[a]Conditions: **1a** (0.2 mmol, 1.0 equiv), **2** (0.4 mmol, 2.0 equiv), catalyst (10 mol %), ligand (12 mol %), $(MeO)_2MeSiH$ (0.6 mmol, 3.0 equiv), CsF (0.6 mmol, 3.0 equiv), DME (4.0 mL, 0.05 M), 12 h, isolated yields. The enantiomeric ratio was determined by HPLC analysis using a chiral stationary phase. Abbreviations: Bn, benzyl. DME, 1,2-dimethoxyethane. DCE, 1,2-dichloroethane. NR, no reaction.

on the reaction's outcome. When KF was employed as the base, the reaction remained feasible, albeit with noticeably less favorable results compared with the use of CsF (Table 1, entry 6). The use of K_3PO_4 proved to be unsuitable for this transformation, resulting in suboptimal yields and selectivity (Table 1, entry 7). These experimental observations underscored the critical role of the base in controlling the reaction's efficiency and selectivity. In addition to assessing various bases, the choice of solvent was also examined for its influence on the reaction. Among the solvents tested, it became evident that DME (dimethoxyethane) emerged as the most suitable solvent for this transformation (Table 1, entry 8−9).

Under the established optimal conditions, we embarked on a thorough exploration of the substrate scope for the amide protected 3-pyrrolines, utilizing CH_3I as a methyl source (Figure 1). Diverse substrates featuring a range of substituents at the ortho-, meta-, and para-positions of the benzene ring were employed. These substituents including electron-donating methyl and methoxy groups, as well as electron-

https://doi.org/10.1021/jacsau.4c00275
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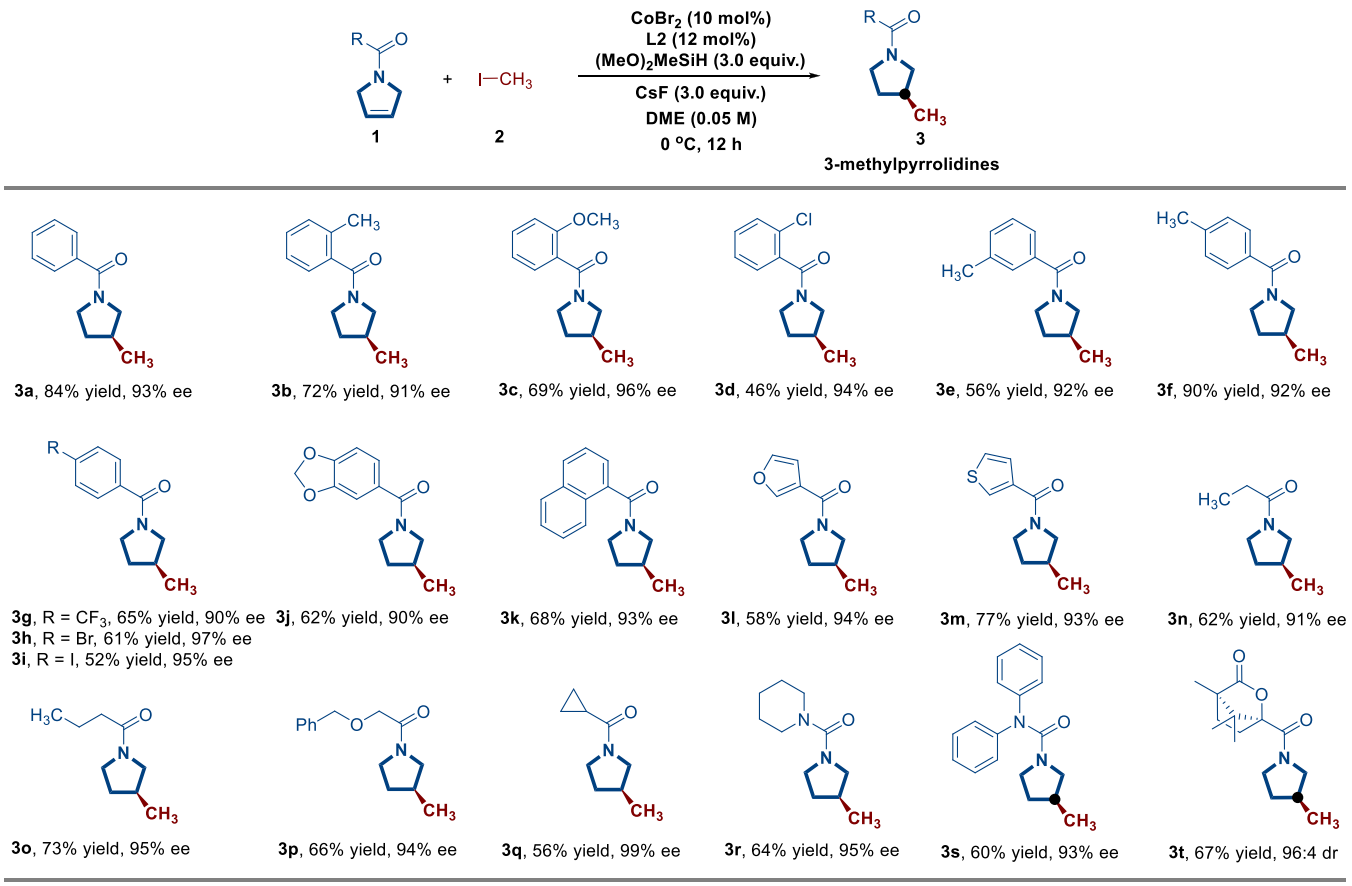

Figure 1. Substrate scope for alkenes.

withdrawing trifluoromethyl, bromo, and iodo groups were well tolerated to yield the target compounds (**3a**−**3i**) in yields spanning from 46 to 90%, with consistently high enantiomeric excess (ee) values ranging from 90 to 97%. Impressively, even substrates bearing methylenedioxy and naphthyl groups were amenable to the reaction, yielding products (**3j**-**3k**) with excellent yields and enantioselectivity. Expanding the substrate scope further, we found that the reaction could be effectively extended to substrates containing furan and thiophene heterocyclic rings (**3l**-**3m**). Moreover, when acyl substrates were derived from aliphatic and cycloalkane substituents, the reaction afforded 3-methyl-modified pyrroline products (**3n**−**3r**) in good yields ranging from 56 to 73%, often accompanied by exceptional enantiomeric excess values of up to 99%. Notably, the reaction showed remarkable tolerance toward substrates featuring substantial steric hindrance (**3s**), delivering the target compound in a 60% yield with a 93% ee value. These results collectively highlight the reaction's versatility and capacity to accommodate diverse substrates while maintaining high selectivity, including those with challenging structural motifs. The excellent functional group tolerance of this reaction was further exemplified through the modification of drugs such as camphoric acid (**3t**), underlining its potential utility in the synthesis of valuable pharmaceutical intermediates.

In the realm of physiological investigation and medical research, stable isotope tracer technology has emerged as a powerful and promising tool. The highly efficient CoH-catalyzed hydromethylation of unactivated olefins, executed under mild conditions, provides an efficient and versatile synthetic methodology for the construction of a variety of key drug intermediates and synthetic building blocks. To demonstrate the broad applicability of this synthetic method in stable isotope tracer technology, we extended our investigation to employ CD_3I and $^{13}CH_3I$ as the methyl source (Figure 2). The asymmetric remote olefin hydromethylation reaction successfully furnished the desired products (**4a**−**4t**) and (**5a**−**5t**) in moderate to high yields, coupled with outstanding enantioselectivities. This extension underscores the adaptability and utility of our method, particularly in the context of stable isotope labeling, enabling the streamlined synthesis of valuable compounds for applications in pharmaceutical research and beyond.

To further explore the efficacy of this direct enantioselective methyl group installation onto molecules in organic synthesis, we redirected our focus to glycochemistry. Following the meticulous optimization of reaction conditions, our investigation yielded promising results with broad applicability (Figure 3). As expected, the hydromethylation process proceeded smoothly across various glycals bearing diverse functional groups. Notably, glycals (**6a**−**6c**) derived from D-glucal exhibited good reactivity with CH_3I, CD_3I or $^{13}CH_3I$ under standard conditions, affording moderate to good yields with outstanding β-selectivity (β/α > 20:1). However, a slightly reduced reaction efficiency was observed with $^{13}CH_3I$ (**9a** and **9b**). Gratifyingly, the substitution of a benzyl group to a naphthyl group has no impact on the reactivity and stereoselectivity of the reaction (**7d**, **8d** and **9d**).

Furthermore, tri-*O*-methyl-D-glucal (**6e**) furnished the corresponding products **7e**, **8e**, and **9e** in moderate yields

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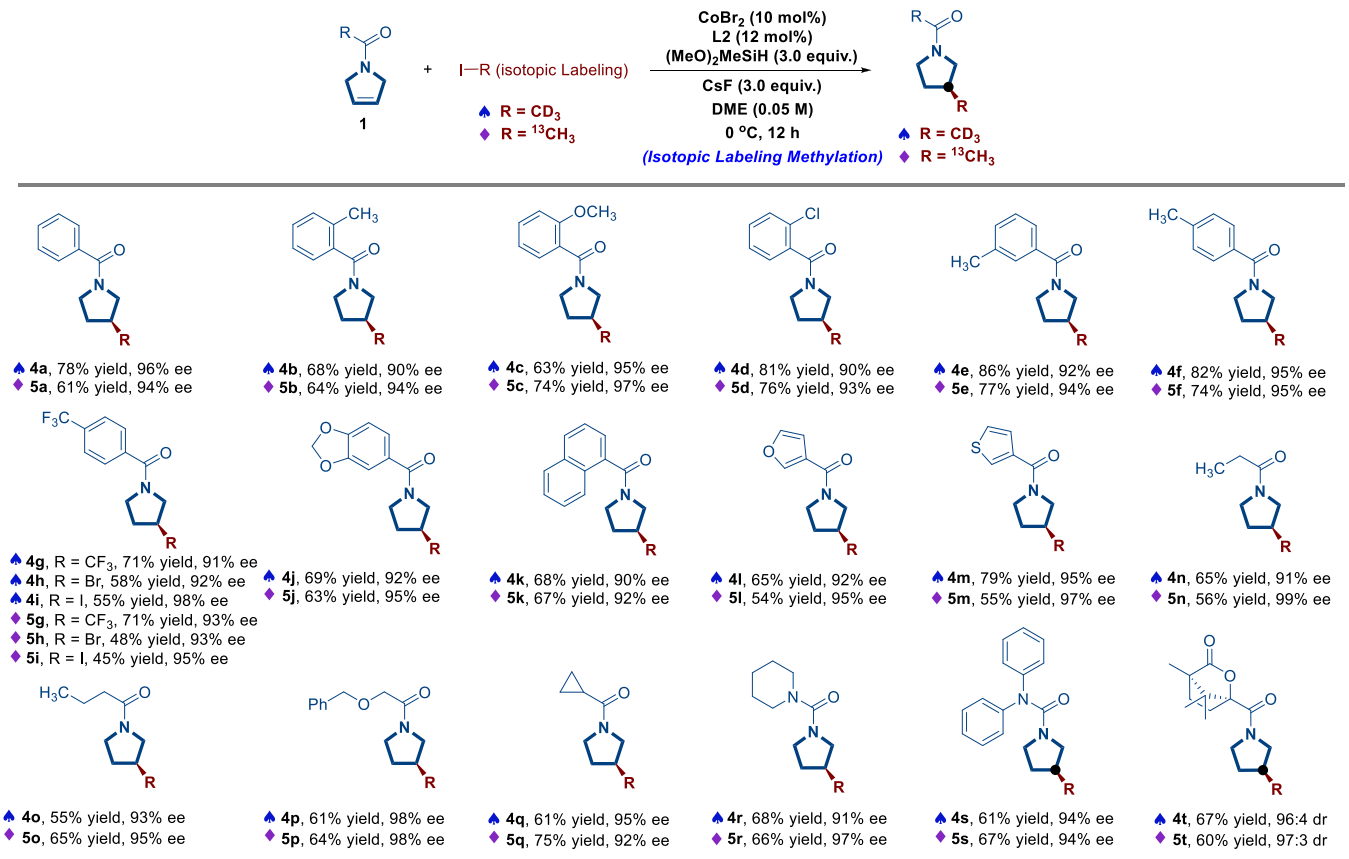

Figure 2. Substrate scope for alkenes.

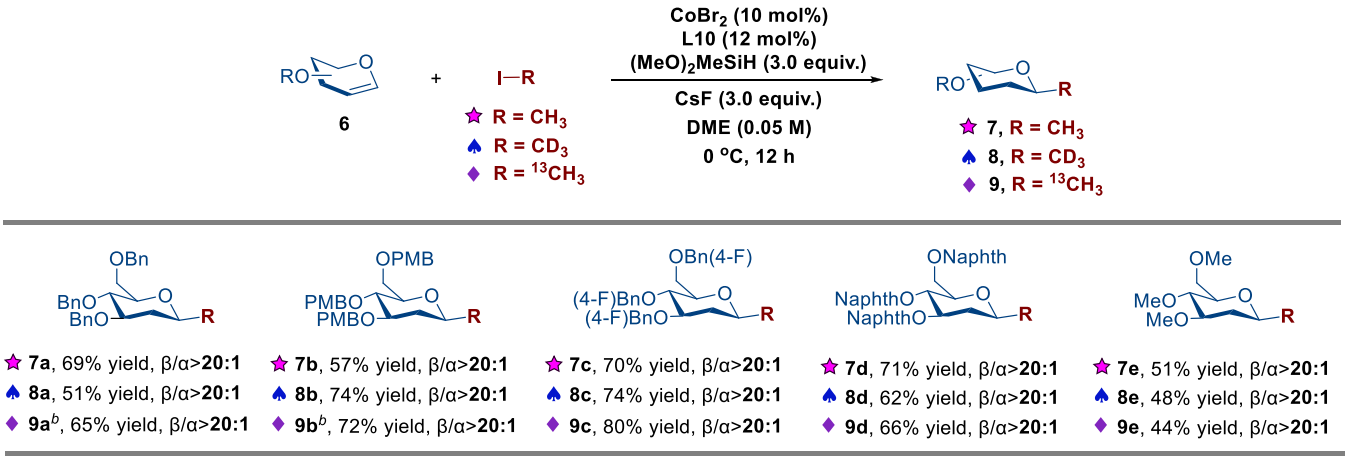

Figure 3. Substrate scope for glycals. [a]Conditions: **6** (0.1 mmol, 1.0 equiv), **2** (0.2 mmol, 2.0 equiv), $CoBr_2$ (10 mol %), **L10** (12 mol %), $(MeO)_2MeSiH$ (0.3 mmol, 3.0 equiv), CsF (0.3 mmol, 3.0 equiv), DME (2.0 mL, 0.05 M), 12 h, isolated yields. [b]Reaction time was extended to 30 h. β/α ratios were determined by ^1H NMR spectroscopy. Abbreviations: Bn, benzyl. Naphth, 1-Naphthyl. PMB, *p*-methoxybenzyl. (4-F)Bn, 4-fluorobenzene.

with consistently excellent β-selectivity (β/α > 20:1), highlighting the good substrate scope of this methodology in glycochemistry.

To evaluate the practical applicability of this reaction, we scaled up the model reaction to 5 mmol and it proceeded smoothly with a 73% yield while maintaining almost the same level of enantioselectivity. Subsequently, we explored the synthetic applications of the C3-methylated pyrrolidine product obtained from this reaction. In the presence of DIBAL-H (diisobutylaluminum hydride), the carbonyl group was efficiently reduced to a methylene group, yielding the benzyl-substituted pyrrolidine product **10a** in 57% yield and 91% ee. Additionally, the asymmetric hydromethylation reaction was suitable for the six-membered cyclic olefin **1u**, although it resulted in a mixture of two regioselective products, **11a** and **11a′**, with a yield of 55%. Given the crucial role of enantioenriched 3-methylpyrrolidine in drug synthesis as a key intermediate for various pharmaceuticals, including CDc7 kinase inhibitors,[2,4] DYRK inhibitors,[5] dipeptidyl peptidase IV inhibitors,[110] antineoplastic drugs,[111] and more, the develop-

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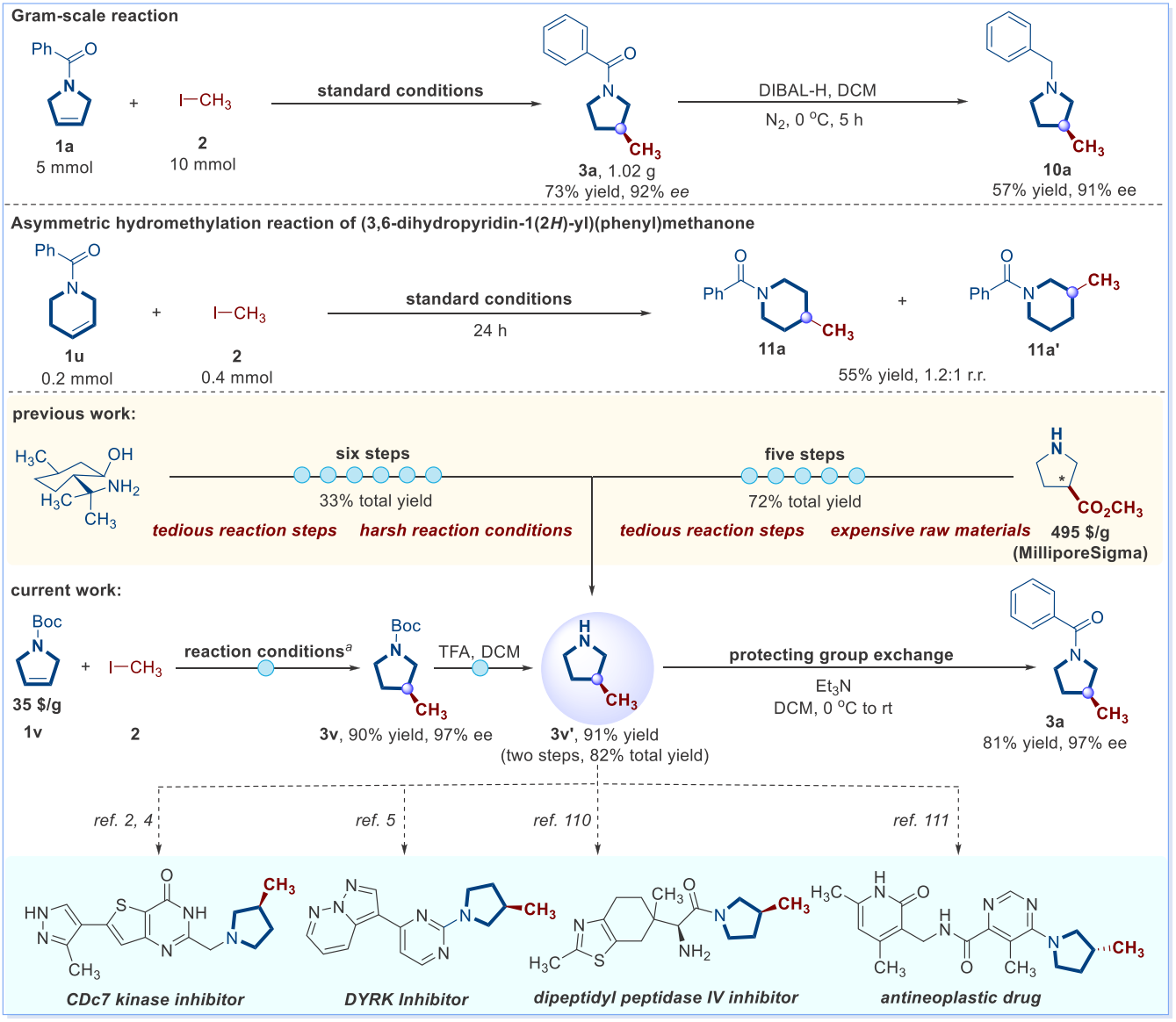

Figure 4. Synthetic applications. [a]Reaction conditions: **1u** (0.2 mmol, 1.0 equiv), **2** (0.4 mmol, 2.0 equiv), $CoBr_2$ (10 mol %), **L7** (12 mol %), $(MeO)_2MeSiH$ (0.6 mmol, 3.0 equiv), CsF (0.6 mmol, 3.0 equiv), DME (4.0 mL, 0.05 M), 12 h, isolated yields.

ment of its synthetic methods is highly desirable. However, traditional synthesis approaches face some limitations, involving either a six-step reaction of chiral amino alcohols or a five-step conversion of expensive chiral 3-carboxylate pyrrolidine as the raw material. These methods, while yielding chiral 3-methylpyrrolidine, suffer from harsh conditions, cumbersome steps, and relatively low overall yields. In contrast, utilizing relatively inexpensive *N*-Boc endocyclic olefins, these CoH-catalyzed enantioselective remote hydromethylation reactions provide a more efficient route. This process yields Boc-protected (*S*)-3-methylpyrrolidine compounds with a high yield and enantioselectivity. Following a single deprotection step, (*S*)-3-methylpyrrolidine was obtained with a total yield of 82%. Remarkably, the protection reaction proceeded smoothly using the benzoyl group, with a high yield and nearly unchanged enantioselectivity, confirming the high operability for the synthesis of various pharmaceuticals from (*S*)-3-methylpyrrolidine with high efficiency (Figure 4).

To gain insight into the reaction mechanism, we conducted preliminary mechanistic investigations. First, radical clock experiments were performed under standard conditions using (2,5-dihydro-1*H*-pyrrol-1-yl)(phenyl)methanone **1a** and radical clock substrates (iodomethyl)cyclopropane **12**. The experiment yielded the ring-opening product **13a** in a 22% yield, suggesting that the reaction proceeds involved a radical process (Figure 5a). Furthermore, the addition of 2,2,6,6-tetramethylpiperidinyloxy (TEMPO) under standard conditions inhibited the reaction, providing further evidence for the involvement of a free radical pathway (Figure 5b). Isotope labeling experiments using Ph_2SiD_2 as the hydrogen source led to the formation of 3-position deuterium-labeled (99% D) products **3a**−**d** in 40% yield, confirming that the hydrogen in the olefins hydromethylation originates from silane and that the migration and insertion of olefins into Co−H are irreversible (Figure 5c). The experimental results indicated that there was no occurrence during the reaction process, *β*-H elimination. Moreover, when 3-pyrroline **1a** was treated under

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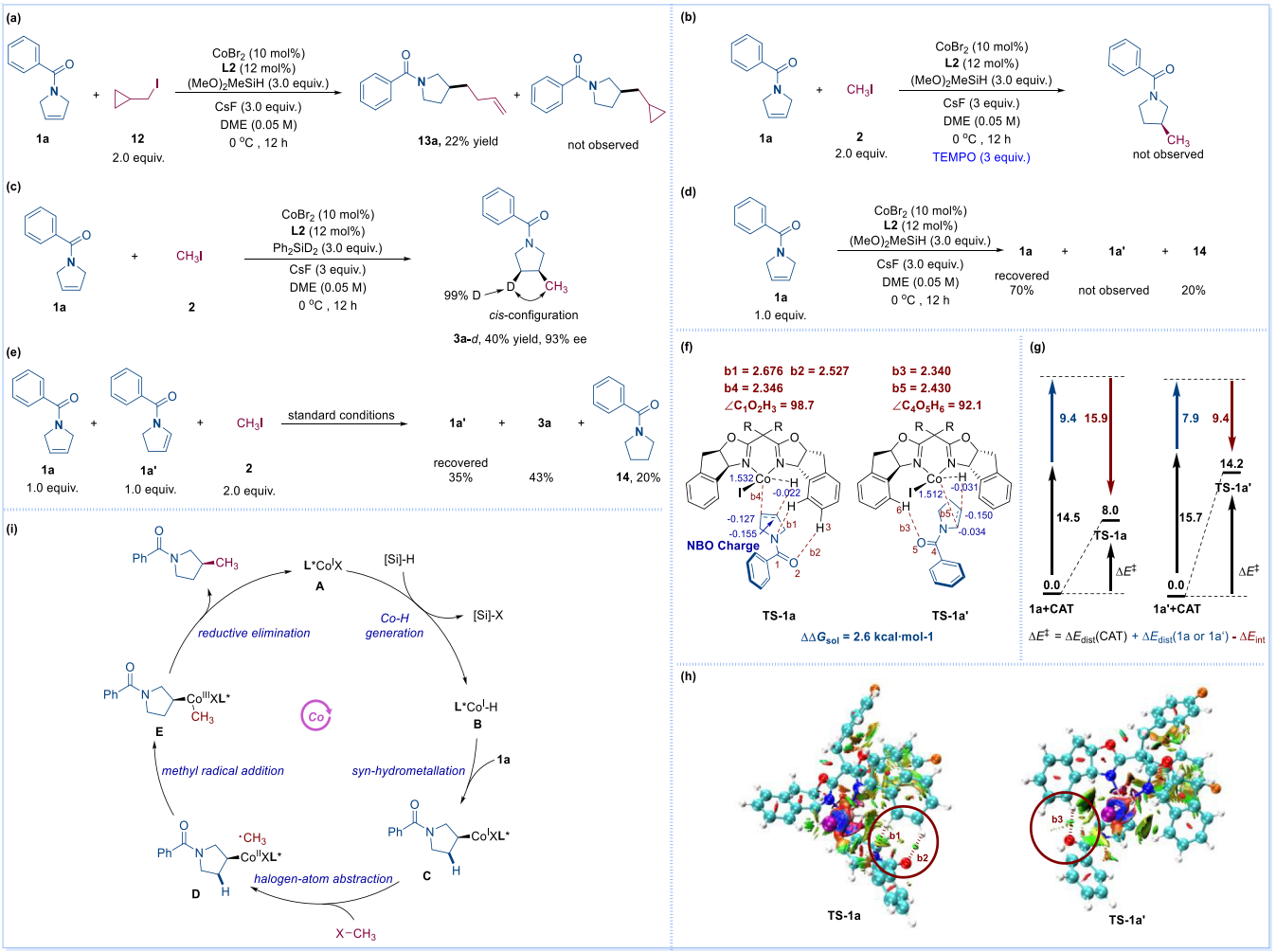

Figure 5. Mechanistic investigations and the proposed mechanism.

standard conditions for 12 h, no double bond migration product **1a′** was detected (Figure 5d). Additionally, the crossover experiment involving 3-pyrroline **1a** and 2-pyrroline **1a′** with iodomethane **2** under standard conditions was conducted, yielding **3a** with a 43% yield. The **1a′** was recovered at a 35% yield, and a 20% reduction byproduct was formed simultaneously (Figure 5e). These experimental results indicated that the desired product **3a** was formed through the direct hydromethylation of **1a**, rather than the formation of the olefin isomerization intermediate **1a′** through chain walking. To better understand the reaction selectivity of substrate **1a** and **1a′**, we also carried out DFT calculations on the migratory insertion process between the Co−H bond and substrates (see more details in the Supporting Information). As shown in Figure 5f, two key transition states **TS-1a** and **TS-1a′** corresponding to the migratory insertion process were located with DFT calculations, and a Gibbs free energy difference of 2.6 kcal mol^{-1} agrees well with the experimentally observed selectivity for substrate **1a**. The energy decomposition analysis in Figure 5g indicates that the energy difference between **TS-1a** and **TS-1a′** could be mainly attributed to the energy difference of the interaction energies (ΔE_{int}) between Co−H and substrates in **TS-1a** and **TS-1a′**. The structural parameters in Figure 5f show that two C−H···X interactions are observed in **TS-1a**. One C−H···N (b_1 = 2.676 Å) and one C−H···O (b_2 = 2.527 Å) interactions in **TS-1a** make this transition state has lower energy than **TS-1a′**, where only one C−H···O (b_3 = 2.340 Å) interaction is observed. These C−H···X interactions could be visualized from the noncovalent interactions plot in Figure 5h. In addition, the NBO charges on the C═C double bond in **TS-1a** are −0.127 and −0.155, while −0.150 and −0.034 in **TS-1a′**. The more negative charges make **TS-1a** has better interactions with positive Co center (1.532 and 1.512 on Co in **TS-1a** and **TS-1a′**), which could stabilize the transition state structure. This strong interaction agrees well with the fact that the bond distance of Co−C in **TS-1a** is 2.346 Å, which is shorter than 2.430 Å in **TS-1a′**. Based on our preliminary mechanistic investigations and relevant literature, we propose a plausible reaction mechanism for this reaction (Figure 5i). Initially, the $Co^{I}X$ intermediate **A** is activated through interactions with silane and CsF, leading to the formation of Co^{I}−H species **B**. Subsequently, this species undergoes alkene hydrometalation with substrate **1a** to generate the intermediate **C**. Following this, a halogen-atom abstraction occurs to produce alkyl cobalt(II) (**D**), which effectively captures the methyl radical, resulting in the formation of dialkyl cobalt(III) (**E**). Then, intermediate **E** engages in a reductive elimination reaction, ultimately yielding product **3a**. Finally, Co^{I}-X intermediate **A** is regenerated to continue to participate in the reaction.

https://doi.org/10.1021/jacsau.4c00275
JACS Au 2024, 4, 2312−2322

CONCLUSIONS

In summary, we have developed a CoH-catalyzed asymmetric hydromethylation strategy, providing precise stereoselective control over the addition of the methyl group for the remote and stereoselective installation of a methyl group onto N-heterocycles. Utilizing a commercial cobalt precursor and a modified bisoxazoline (BOX) ligand enables the conversion of easily accessible 3-pyrrolines to valuable enantiopure 3-(isotopic labeling)methylpyrrolidine compounds with excellent enantioselectivity. This method exhibits broad substrate universality, good functional group tolerance, and exceptional compatibility with isotopically labeled substrates such as CD_3I and $^{13}CH_3I$. The practicality of this protocol is demonstrated through the streamlined two-step synthesis of enantioenriched 3-methylpyrrolidine from relatively inexpensive *N*-boc endocyclic olefins, replacing a process that previously required up to five or six steps with harsh reaction conditions or expensive starting materials. The DFT calculations further confirm the importance of choosing cobalt as the catalytic metal in the reaction, promoting the direct hydromethylation of **1a** to generate the desired product **3a** rather than forming C_2-methylated pyrroline byproducts through the olefin isomerization intermediate **1a′** via chain walking.

METHODS

General Procedure for Cobalt-Catalyzed Enantioselective Hydromethylation of Olefins

To an oven-dried 10 mL Schlenk tube containing a stirring bar was charged with $CoBr_2$ (0.02 mmol, 10 mol %), ligand (0.024 mmol, 12 mol %), and 2.0 mL of dry 1,2-dimethoxyethane in a nitrogen-filled glovebox; the mixture was stirred for 10 min at room temperature. Then *N*-acyl endocyclic olefins (0.2 mmol, 1.0 equiv) or glycal (0.2 mmol, 1.0 equiv), iodomethane (0.4 mmol, 2.0 equiv), CsF (0.6 mmol, 3.0 equiv), and another 2.0 mL dry 1,2-dimethoxyethane were added sequentially. The tube was sealed and removed from the glovebox, $(MeO)_2MeSiH$ (0.6 mmol, 3.0 equiv) was added dropwise at 0 °C and the reaction was stirred at 0 °C for 12 h. After the reaction was completed, the reaction mixture was diluted with saturated NH_4Cl (aq, 2.0 mL) and EtOAc (5.0 mL). The aqueous phase was extracted with EtOAc (2× 5.0 mL). The organic phase was dried over Na_2SO_4, filtered, and the solvent was removed in vacuo. The crude mixture was purified by flash column chromatography on silica gel using a mixture of hexane/EtOAc as eluent to obtain the desired product.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org.

Experimental procedures, characterization data, copies of NMR spectra, and HPLC traces of enantioenriched products (PDF)

Accession Codes

CCDC 2306491 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.

ACKNOWLEDGMENTS

We are grateful for the generous financial support from the National Natural Science Foundation of China (21801206), Shaanxi Fundamental Science Research Project for Chemistry & Biology (22JHQ002), and the Program for Young Talents of Shaanxi Province (5113190023), the Innovation Foundation for Doctor Dissertation of Northwestern Polytechnical University (CX2023104), Natural Science Basic Research Program of Shaanxi (2024JC-ZDXM-08) and the Fundamental Research Funds for the Central Universities (05150-24GZ210101). S.-F.N. acknowledge funding from the STU Scientific Research Foundation for Talents (NTF20022).

https://doi.org/10.1021/jacsau.4c00275
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https://doi.org/10.1021/jacsau.4c00275
JACS Au 2024, 4, 2312−2322