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Enantioselective Radical Cyclization for Construction of 5-Membered Ring Structures by Metalloradical C–H Alkylation

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Abstract

Radical cyclization represents a powerful strategy for construction of ring structures. Traditional radical cyclization, which is based on radical addition as the key step, necessitates the use of unsaturated substrates. Guided by the concept of metalloradical catalysis, a different mode of radical cyclization that can employ saturated C–H substrates is demonstrated through the development of a Co(II)-based system for catalytic activation of aliphatic diazo compounds for enantioselective radical alkylation of various C(sp³)–H bonds. It allows for efficient construction of chiral pyrrolidines and other valuable 5-membered cyclic compounds. This alternative strategy of radical cyclization provides a new retrosynthetic paradigm to prepare five-membered cyclic molecules from readily available open-chain aldehydes through the union of C–H and C=O elements for C–C bond formation.

Alkyl radicals have been extensively explored as versatile intermediates for chemical synthesis.¹ Among applications, alkyl radicals have been demonstrated to undergo radical cyclization for construction of ring structures via C–C bond formation.¹ Though numerous radical cyclization reactions have been implemented with alkyl radicals,² they are predominantly based on radical addition to multiple bonds as the key step, followed by further transformations such as H atom abstraction (RA-HAA) (Scheme 1a). Consequently, traditional radical cyclization necessitates the use of unsaturated substrates such as alkenes. Besides the established RA-HAA cyclization, it is conceivable that the combination of H

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ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.8b01662.

Experimental details and analytical data for all new compounds (PDF)

Data for C₁₅H₂₀BrNO₂ (CIF)

Data for C₁₆H₂₃NO₂ (CIF)

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atom abstraction and radical substitution (HAA-RS) could give rise to an alternative C—C bond forming pathway for radical cyclization that could employ saturated C—H substrates (Scheme 1b). Though HAA is normally facile, RS at the carbon has been recognized as an inherently challenging pathway due to a highly organized transition state involving three multisubstituted carbon centers.^{1a,3} Therefore, this alternative radical cyclization, although seemingly tenable, is largely undocumented for alkyl radicals. One potential solution would be the introduction of α -metalloalkyl radicals $R_2(L_nM)-C\cdot$, where one of the substituents of common alkyl radicals is replaced by a metal complex (ML_n) (Scheme 1c). Because M—C bonds are typically more polar and weaker than C—C bonds, the radical substitution pathway would become both thermodynamically and kinetically possible.⁴ Furthermore, this metalloradical-based cyclization could be potentially rendered as a catalytic process with possible control of enantioselectivity, allowing for stereoselective construction of cyclic compounds from C—H substrates.

To harness the potential of radical reactions for stereoselective organic synthesis,⁵ metalloradical catalysis (MRC) has recently been introduced as a conceptually new approach for addressing some enduring challenges.^{6,7} MRC aims at the development of metalloradical complexes as open-shell catalysts for generation of metal-supported organic radicals and for control of their subsequent homolytic reactions. As stable metalloradicals, Co(II) complexes of D_2 -symmetric chiral amidoporphyrins [$Co(D_2\text{-Por}^*)$] exhibit the unusual capability of activating diazo compounds to generate α -Co(III)-alkyl radicals.⁸ The α -metalloalkyl radicals can undergo radical addition and H atom abstraction as well as subsequent radical substitution, leading to invention of new catalytic systems for various stereoselective radical transformations.⁹ Among them, we recently illustrated the aforementioned radical cyclization strategy with stereoselective formation of sulfolanes from α -methoxycarbonyl- α -diazosulfones.^{9b} To demonstrate synthetic utility of this new mode of radical cyclization via Co(II)-based MRC, we were intrigued if linear aliphatic diazo compounds, which are typically generated in situ from sulfonyl hydrazones of the corresponding carbonyl precursors due to their instability, could be employed for the asymmetric synthesis of common ring structures, such as pyrrolidines, tetrahydrofurans, and other important 5-membered cyclic compounds (Scheme 2a). Mechanistically, it was unclear if aliphatic diazo compounds could be activated by [$Co(D_2\text{-Por}^*)$] to form the corresponding α -Co(III)-alkyl radicals **I**. If so, could the rate of the metalloradical activation match with their in situ-generation? Could α -Co(III)-alkyl radicals **I**, which possess β -hydrogens, proceed 1,5-HAA to generate ϵ -Co(III)-alkyl radicals **II** competitively over the potential β -H atom shift? Additional questions arose from the flexible nature of the linear alkyl chain that could pose extra challenges in achieving stereoselective construction of the 5-membered structures. Without conformational rigidity, would the intermediate **II** be capable of undergoing effective 5-*exo-tet* radical cyclization? What determinant factors could be explored for controlling the enantioselectivity of C—C bond forming process? We reasoned that the key to address these and related challenges is to develop suitable D_2 -symmetric chiral amidoporphyrin ligand ($D_2\text{-Por}^*$) that directs the Co(II)-based catalysis for productive cyclization. If realized, it would provide a general strategy for stereoselective radical synthesis of five-membered cyclic molecules from aliphatic aldehyde-derived hydrazones. This mode of radical cyclization based on metalloradical C—H alkylation would offer a new

retrosynthetic paradigm for construction of ring structures where C—C bond can be disconnected as common C=O and C—H units of open-chain aldehydes (Scheme 2b).

Chiral pyrrolidines containing α -substituent are recurring core structures in natural products and bioactive compounds (Figure S1). Considerable efforts have been devoted to devise strategies for their asymmetric synthesis. Though the existing catalytic systems mostly involve functionalization of preformed pyrrolidine rings,¹⁰ there has been no previous report on asymmetric construction of α -substituted chiral pyrrolidines via catalytic C—H alkylation with acyclic aliphatic diazo compounds.¹¹ As a demonstration of HAA-RS radical cyclization, we report the development of a new Co(II)-based catalytic system that is highly efficient for stereoselective synthesis of α -substituted pyrrolidines and other common 5-membered compounds from aliphatic diazo compounds by enantioselective intramolecular radical alkylation of various C(sp³)—H bonds. In addition to chemoselectivity and regioselectivity, this new radical cyclization features functional group tolerance and heteroarene compatibility.

Aliphatic aldehyde-derived tosylhydrazone **1a** was chosen as the model substrate to test the proposed radical cyclization (Table 1). The achiral metalloradical catalyst [Co(**P1**)] (**P1** = 3,5-Di^tBu-IbuPhyrin)¹² could catalyze the reaction to afford 2-phenylpyrrolidine (**2a**) in 81% yield, demonstrating the feasibility of the HAA-RS pathway. The high yield indicated that the in situ-generated aliphatic diazo compound could be effectively incorporated into the catalytic cycle. When chiral metalloradical catalyst [Co(**P2**)] (**P2** = 3,5-Di^tBu-ChenPhyrin) was employed,^{9g} the radical cyclization exhibited almost no asymmetric induction despite the high yield (entry 2). Considering the flexible nature of the linear alkyl chain, this negative result was not unexpected. To reduce the degree of conformational freedom of the Co(III)-alkyl radical intermediates, we decided to crowd the steric environment of the ligand pocket. Indeed, the employment of [Co(**P3**)] (**P3** = 2,6-DiMeO-ChenPhyrin) resulted in significant asymmetric induction without affecting the reactivity (entry 3). To further this buttressing effect, [Co(**P4**)] (**P4** = 3,5-Di^tBu-ZhuPhyrin), which was previously shown to have a more rigid conformation,^{9e} was used. As expected, it could catalyze the reaction in similarly high yield with substantially improved enantioselectivity (entry 4). Subsequent use of [Co(**P5**)] (**P5** = 2,6-DiMeO-ZhuPhyrin) resulted in further increase in both yield and enantioselectivity (entry 5). These results prompted us to synthesize 2,4,6-TriMe-ZhuPhyrin ligand (**P6**), a new derivative of ZhuPhyrin series, where even more sterically demanding mesityl groups are attached at two achiral *meso*-positions. Remarkably, [Co(**P6**)] could catalyze the enantioselective radical C—H alkylation, affording the cyclization product **2a** in 93% yield with 92% *ee* (entry 6; also see Table S1).

The substrate scope of [Co(**P6**)]-catalyzed radical cyclization was evaluated by employing aliphatic aldehyde-derived tosylhydrazone substrates **1** containing different types of C—H bonds (Table 2). As demonstrated with substrates **1a–1j**, benzylic C—H bonds with varied electronic and steric properties could be alkylated to afford 2-arylpiperidines **2a–2j** in high yields with excellent enantioselectivities. The absolute configuration of the major enantiomer of **2f** was established as (*S*). In addition to CN, NO₂, and halogen functionalities, the alkylation could tolerate vinyl groups as exemplified with the formation of **2k** from **1k**. Similarly, the Co(II)-based system could undergo allylic C—H alkylation with high

chemoselectivity, as demonstrated by the formation of 2-vinylpyrrolidine (**2l**) from **1l**. Likewise, propargylic C—H substrate **1m** also underwent the alkylation, giving 2-(phenylethynyl)pyrrolidine (**2m**) chemoselectively. Furthermore, with the stabilization of the α -Co(III)-alkyl radical intermediate **II** by the adjacent heteroatom, this system was applicable for even nonactivated C—H bonds. For example, [Co(**P6**)] could regioselectively alkylate the stronger homobenzylic over the weaker benzylic C—H bonds in substrate **1n**, forming the five-membered pyrrolidine **2n** in 96% yield albeit moderate enantioselectivity. This remarkable regioselectivity indicated that the corresponding α -Co(III)-alkyl radicals **I** (Scheme 2a) had a strong preference for 1,5- over 1,6-H abstraction. In a similar fashion, the system underwent regioselective 1,5-alkylation of stronger secondary C—H bonds in the presence of weaker tertiary C—H bond as illustrated with formation of 2-cyclohexylpyrrolidine (**2o**) from **1o**. Notably, this radical cyclization was even suitable for electron-deficient C—H bonds, as demonstrated by the formation of naturally occurring L-proline ester **2p** in 56% yield with 82% *ee*.

The radical cyclization was also compatible with substrates containing various heteroarenes, allowing for stereoselective construction of α -heteroarylpyrrolidines (Figure S1).¹⁰ For example, 3-pyridine-based precursor **1q** could be effectively activated by [Co(**P6**)] to construct the nicotine derivative **2q** in 73% yield with 92% *ee*.

Its major enantiomer was confirmed to have the same (*S*) absolute configuration as naturally occurring nicotine.^{10c} Use of 2- and 4-pyridine-based hydrazones **1r** and **1s** permitted the synthesis of α - and γ -nicotine derivatives **2r** and **2s**, respectively. Likewise, this alkylation could be applied for both quinoline- and indole-based substrates **1t** and **1u** to form the corresponding α -heteroarylpyrrolidines. Furthermore, chiral pyrrolidines containing α -thiophene (**2v**) and α -benzothiophene (**2w**) were efficiently constructed. Notably, the reaction could be scaled up as demonstrated with the high-yielding synthesis of **2w** on 2.0 mmol scale without affecting the enantioselectivity. Interestingly, the C—H bond adjacent to the cyclopentadienyl ring of ferrocene-based substrate **1x** could be selectively alkylated to form the chiral α -ferrocenylpyrrolidine **2x** in 53% yield with 92% *ee*, which has potential applications as a chiral ligand.¹³

Preliminary results showed this radical cyclization strategy could also be applied for construction of other common five-membered ring structures. For example, [Co(**P6**)] could catalyze intramolecular C—H alkylation of both ether- and thioether-linked diazo precursors **1y** and **1z** for radical cyclization, forming α -phenyltetrahydrofuran (**2y**) and α -phenyltetrahydrothiophene (**2z**), respectively, in good yields with high enantioselectivities. Furthermore, the cyclization even allowed for direct formation of cycloalkanes from diazo precursors with flexible all-methylene linkers, as exemplified by the high-yielding synthesis of phenylcyclopentane (**2aa**) from 5-phenylpentanal tosylhydrazone (**1aa**). Actually, 5-membered cyclic compounds with varied substitution patterns could be accessed in a similar fashion from diazo precursors derived from aliphatic aldehydes with different linkers, as demonstrated by formation of β -substituted pyrrolidine **2ab** from substrate **1ab**.

Several experiments were performed to shed light on the underlying mechanism of the Co(II)-catalyzed process (Scheme 3). First, monodeuterated **1a–D** was synthesized to

measure the intramolecular kinetic isotope effect (KIE) (Scheme 3a). ^1H NMR analysis of the product mixture revealed $k_{\text{H}}/k_{\text{D}} = 9.2/1$ (Figure S2). This high level of primary KIE conforms with the proposed C—H activation via HAA by α -Co(III)-alkyl radical intermediate I (Scheme 2a). Second, the effect of TEMPO on the C—H alkylation was examined for the reaction of **1t** by [Co(P1)] (Scheme 3b). Though no alkylation product **2t** was observed, it produced the TEMPO-trapped compound **3t**. The observation of **3t** supports the existence of ε -Co(III)-alkyl radical intermediate II, which was apparently trapped by two molecules of TEMPO at the α - and ε -carbon centers (Figure S3). Third, the enantiopure (*R*)-**4a** was prepared to evaluate the stereochemistry of the catalytic alkylation by the achiral catalyst [Co(P1)] (Scheme 3c). The tertiary C—H bond was alkylated to form α,α -disubstituted pyrrolidine **5a** as a mixture of enantiomers. Chiral HPLC analysis showed that (*S*)-**5a** was the major enantiomer with 81% *ee*. The results indicate that the resulting radical intermediate II from HAA of (*R*)-**4a** underwent radical substitution with retention of stereochemistry at a much faster rate than racemization (Figure S4). Last, the Co(III)-supported alkyl radical intermediates from the reaction of **1a** by [Co(P1)] could be directly detected by HRMS (Figure S5) and trapped by phenyl *N-tert*-butylnitrone (PBN) to give the characteristic EPR signal (Figure S6). Together, these results support the stepwise radical mechanism for Co(II)-based cyclization through metalloradical C—H alkylation (Scheme 2a).

In summary, we have broadened the applicability of the newly emerged radical cyclization mode via metalloradical catalysis (MRC), which involves sequential radical H-atom abstraction and radical substitution (HAA-RS), as a catalytic C—C bond forming strategy for stereoselective construction of pyrrolidines and other common 5-membered cyclic compounds from C—H substrates. This alternative radical cyclization, which is fundamentally different from the traditional radical cyclization of unsaturated substrates involving sequential radical addition and H-atom abstraction (RA-HAA), provides a new retrosynthetic paradigm to synthesize five-membered chiral cyclic molecules from readily available open-chain aldehydes via enantioselective C—C bond formation through the union of C—H and C=O units.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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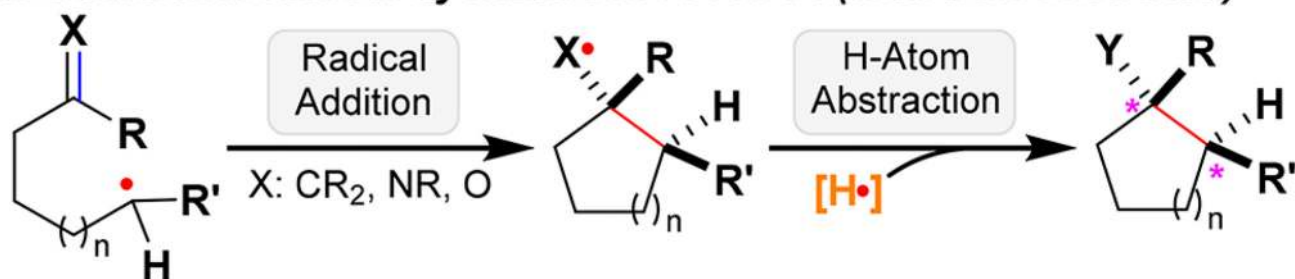
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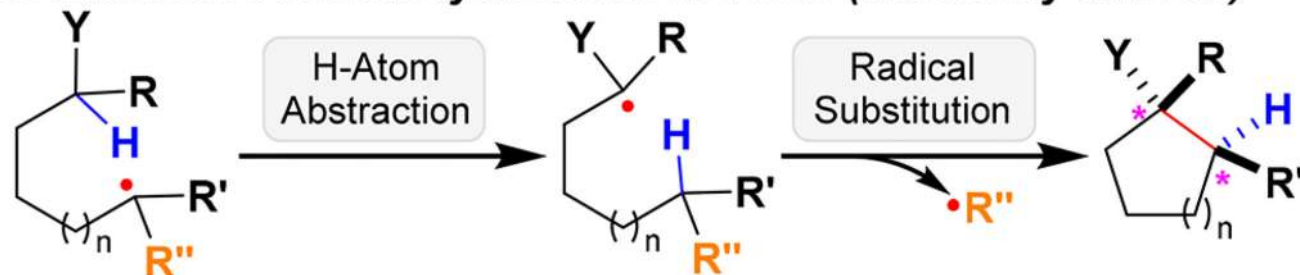
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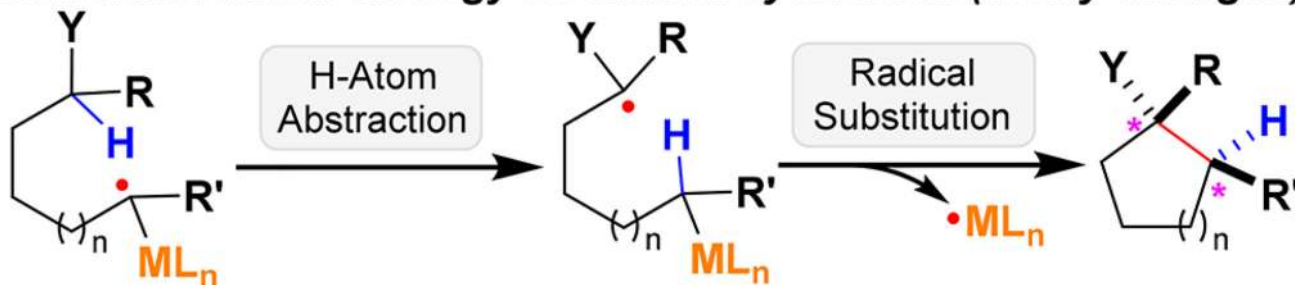
a. traditional radical cyclization: RA-HAA (well demonstrated)



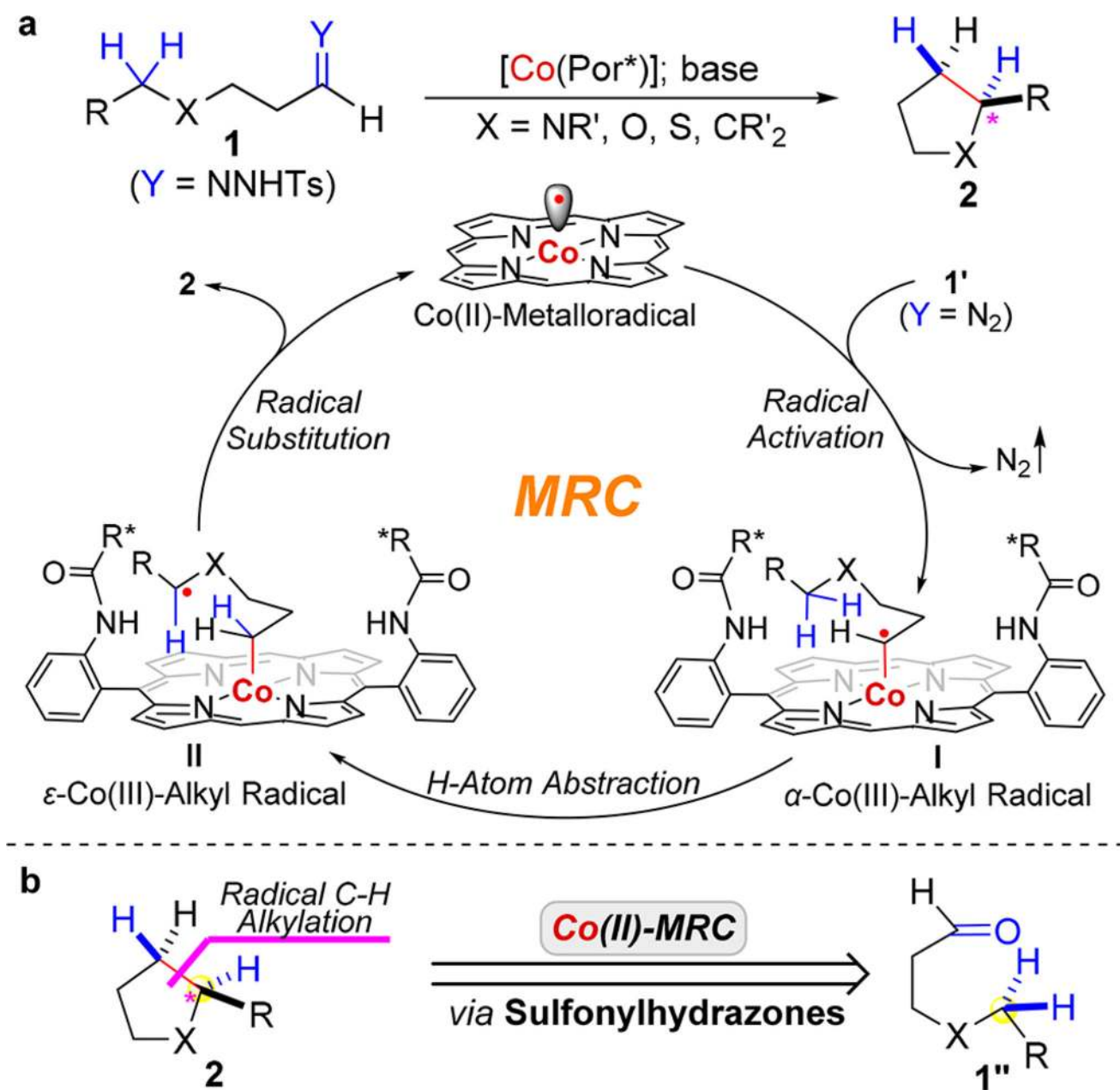
b. alternative radical cyclization: HAA-RS (inherently difficult)



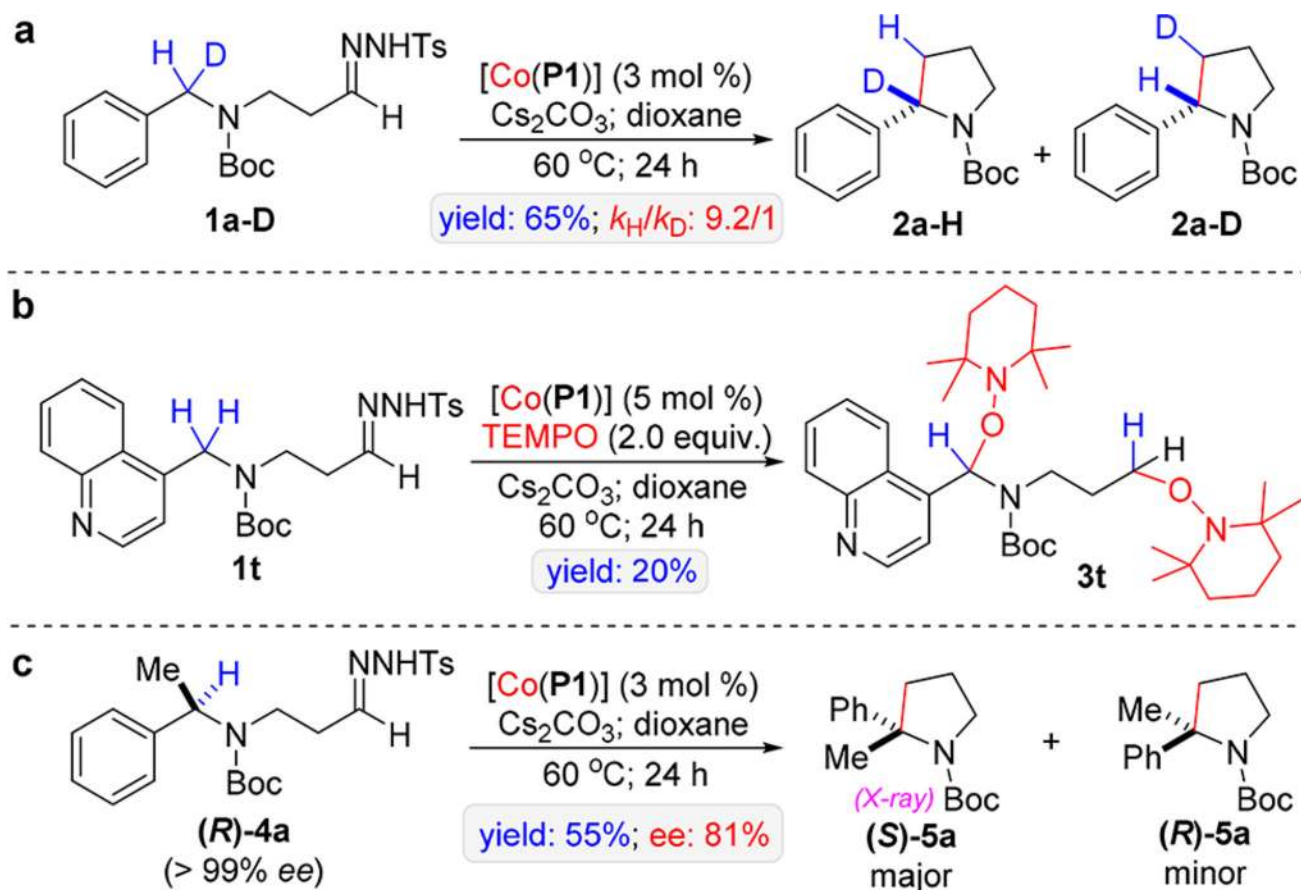
c. metalloradical strategy for radical cyclization (newly emerged)



Scheme 1.
Radical Cyclization Pathways via C—C Bond Formation



Scheme 2.
Proposed Radical Cyclization Mechanism via Metalloradical C—H Alkylation:
Construction of Five-Membered Ring Structures from Open-Chain Aldehydes



Scheme 3.
 Mechanistic Studies for Co(II)-Catalyzed Stepwise Radical Cyclization

Enantioselective Radical Cyclization for α -Substituted Pyrrolidines via [Co(P6)]-Catalyzed C—H Alkylation^a