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New Catalytic Radical Process Involving 1,4-Hydrogen Atom Abstraction: Asymmetric Construction of Cyclobutanones

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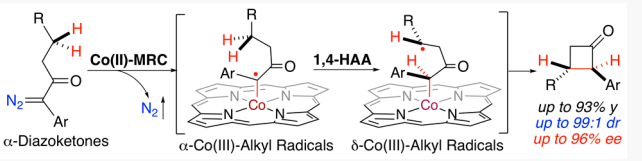
ABSTRACT: While alkyl radicals have been well demonstrated to undergo both 1,5- and 1,6-hydrogen atom abstraction (HAA) reactions, 1,4-HAA is typically a challenging process both entropically and enthalpically. Consequently, chemical transformations based on 1,4-HAA have been scarcely developed. Guided by the general mechanistic principles of metalloradical catalysis (MRC), 1,4-HAA has been successfully incorporated as a key step, followed by 4-*exo*-*tet* radical substitution (RS), for the development of a new catalytic radical process that enables asymmetric 1,4-C−H alkylation of diazoketones for stereoselective construction of cyclobutanone structures. The key to success is the optimization of the Co(II)-based metalloradical catalyst through judicious modulation of D_2-symmetric chiral amidoporphyrin ligand to adopt proper steric, electronic, and chiral environments that can utilize a network of noncovalent attractive interactions for effective activation of the substrate and subsequent radical intermediates. Supported by an optimal chiral ligand, the Co(II)-based metalloradical system, which operates under mild conditions, is capable of 1,4-C−H alkylation of α-aryldiazoketones with varied electronic and steric properties to construct chiral α,β-disubstituted cyclobutanones in good to high yields with high diastereoselectivities and enantioselectivities, generating dinitrogen as the only byproduct. Combined computational and experimental studies have shed light on the mechanistic details of the new catalytic radical process, including the revelation of facile 1,4-HAA and 4-*exo*-*tet*-RS steps. The resulting enantioenriched α,β-disubstituted cyclobutanones, as showcased with several enantiospecific transformations to other types of cyclic structures, may find useful applications in stereoselective organic synthesis.



INTRODUCTION

In the past decades, radical reactions have attracted the growing attention of synthetic organic chemists in view of their rich reactivities and attractive characteristics.[1] Notably, hydrogen atom abstraction (HAA) by free radicals has long been recognized as one of the most general pathways for C−H activation,[2] a fundamental radical reaction that can potentially be utilized for direct functionalization of prevalent C−H bonds in organic molecules. However, the realization of this immense potential faces longstanding challenges that are associated with governing reactivity as well as controlling selectivity of the departing radicals from HAA for ensuing bond formation. To address this and related challenges, metalloradical catalysis (MRC) provides a conceptually new approach for achieving controllable reactivity and selectivity in radical reactions through catalytic generation as well as subsequent regulation of metal-stabilized organic radical.[3−5] As stable 15e-metalloradicals, Co(II) complexes of D_2-symmetric chiral amidoporphyrins [Co(D_2-Por*)] enjoy the unique capability of activating diazo compounds homolytically to generate α-Co(III)-alkyl radicals.[6] These Co-stabilized C-centered radical intermediates can undergo common radical reactions, such as radical addition and hydrogen atom abstraction as well as following radical substitution, leading to new catalytic processes for stereoselective radical transformations.[7] In particular, Co(II)-based MRC was successfully applied for the development of enantioselective radical C−H alkylation of diazo compounds involving 1,5-HAA as the key step for stereoselective construction of 5-membered ring structures.[8] To broaden the synthetic applications of Co(II)-MRC for solving more challenging problems, we were intrigued by the possibility of constructing strained 4-membered ring structures such as cyclobutanones through radical 1,4-C−H alkylation of α-aryldiazoketones (Scheme 1). However, this proposed radical process presented several potential challenges. In view of their unique electronic and steric properties compared with other types of diazo compounds, it was uncertain whether donor/acceptor-substituted diazo compounds **1** could be effectively activated by [Co(D_2-Por*)] to generate the corresponding α-Co(III)-alkyl radicals **I**. Given that 1,4-HAA is known to be an inherently challenging process due to both unfavorable entropic and enthalpic factors,[9] how could the resulting tertiary radical intermediate **I** be promoted for the desired intramolecular hydrogen atom abstraction to form δ-

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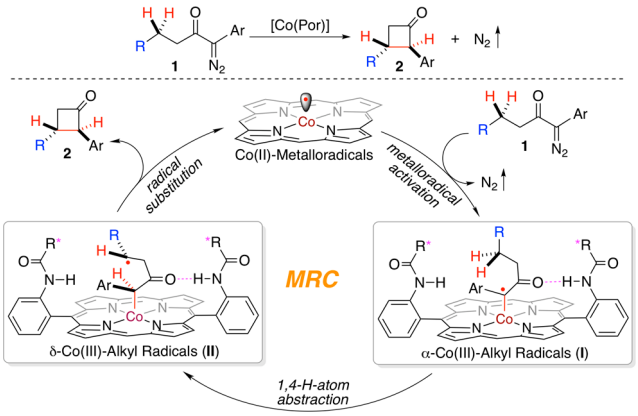
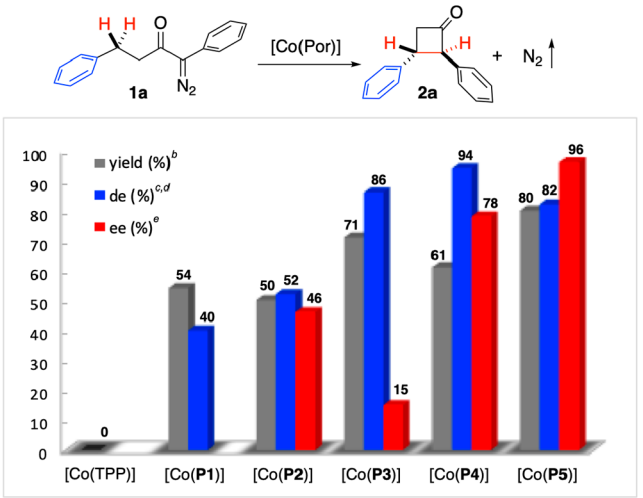
Scheme 1. Working Proposal for Construction of Cyclobutanones by Radical 1,4-C−H Alkylation via Co(II)-Based Metalloradical Catalysis

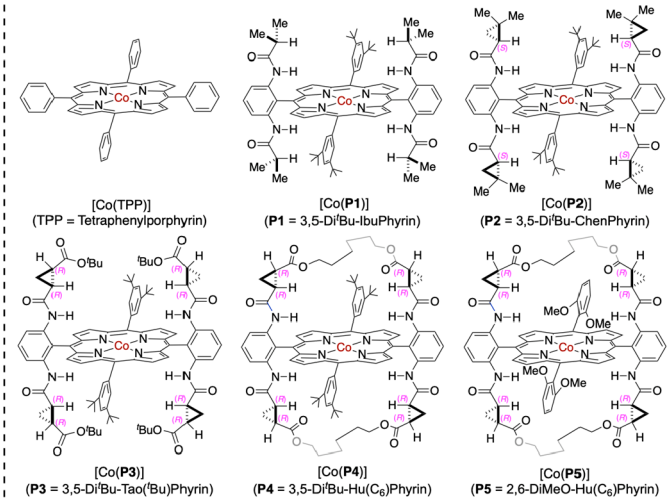


Co(III)-alkyl radicals **II**? Apart from the reactivity concerns, could the 1,4-HAA of α-Co(III)-alkyl radicals **I** be rendered enantioselective? Furthermore, the subsequent 4-*exo*-*tet* radical cyclization of the alkyl radicals **II** via intramolecular radical substitution was expected to be equally challenging in light of the high strain associated with four-membered transition state. What factors could be utilized to facilitate the ring closure for product formation? Additionally, how could the C−C bond formation be achieved with effective diastereoselective control during radical cyclization? We reasoned that all these and related questions could be potentially addressed through the optimization of [Co(D_2-Por*)] catalyst by the fine-tuning of the D_2-symmetric chiral amidoporphyrin ligand to adopt suitable environments that govern the course of the catalytic radical process (Scheme 1). If realized successfully, it would give rise to the first catalytic radical process for asymmetric intramolecular C−H alkylation involving 1,4-HAA as the key step for stereoselective construction of highly strained cyclobutanone structures, the four-membered carbocycles that are important moieties in natural products and pharmaceuticals (Figure S1).[10]

Catalytic asymmetric intramolecular 1,4-C−H alkylation of diazo compounds represents a potentially attractive strategy for the stereoselective construction of four-membered cyclic compounds.[11] Due to the high strain associated with four-membered ring structures, the catalytic process for 1,4-C−H alkylation has been largely underdeveloped. While there have been a few reports on the asymmetric synthesis of β-lactams[12] and β-lactones[13] from α-diazoamides and α-diazoesters, respectively, by Ru, Rh, and Ir-based catalytic systems, asymmetric synthesis of cyclobutanones via 1,4-C−H alkylation from α-diazoketones has not been previously realized.[14] The absence of a catalytic system for cyclobutanone synthesis is presumably attributed to the augmented challenge of 1,4-C−H alkylation for α-diazoketones because of their relatively higher conformational flexibility than α-diazoamides and α-diazoesters. As an exciting new application of Co(II)-based MRC for stereoselective organic synthesis, we herein report the development of the first catalytic system that is highly effective for asymmetric 1,4-C−H alkylation of α-diazoketones to construct chiral cyclobutanones. Supported by a new-generation D_2-symmetric chiral amidoporphyrin ligand, the Co(II)-based metalloradical system, which enjoys operational simplicity and mild conditions, can activate α-aryldiazoketones with varied electronic and steric properties for 1,4-alkylation of C(sp^3)−H bonds, enabling stereoselective construction of chiral α,β-disubstituted cyclobutanones. We show the importance of catalyst development through the fine-tuning of the ligand environments in achieving high reactivity and stereoselectivity in this new radical process. Furthermore, our combined experimental and computational studies on the mechanism of the Co(II)-based metalloradical system have shed light on the underlying stepwise radical pathway, including the key steps of 1,4-HAA and 4-*exo*-*tet*-RS. A series of further transformations of the resulting enantioenriched α,β-disubstituted cyclobutanones are provided to showcase their synthetic applications.

Scheme 2. Ligand Effect on Co(II)-Based Catalytic System for Asymmetric 1,4-C−H Alkylation of α-Aryldiazoketone[a]





[a]Carried out with **1a** (0.10 mmol) using [Co(Por)] (2 mol %) in *tert*-butyl methyl ether (TBME) (0.5 mL) at 40 °C for 12 h. [b]Isolated yield. [c]Diastereomeric excess (de) determined by ^{1}H NMR analysis of crude reaction mixture before purification. [d]Isomerized to *trans*-enriched products with 96% de after purification by silica gel column chromatography for all catalytic reactions. [e]Enantiomeric excess (ee) of *trans*-diastereomer determined by chiral HPLC after purification

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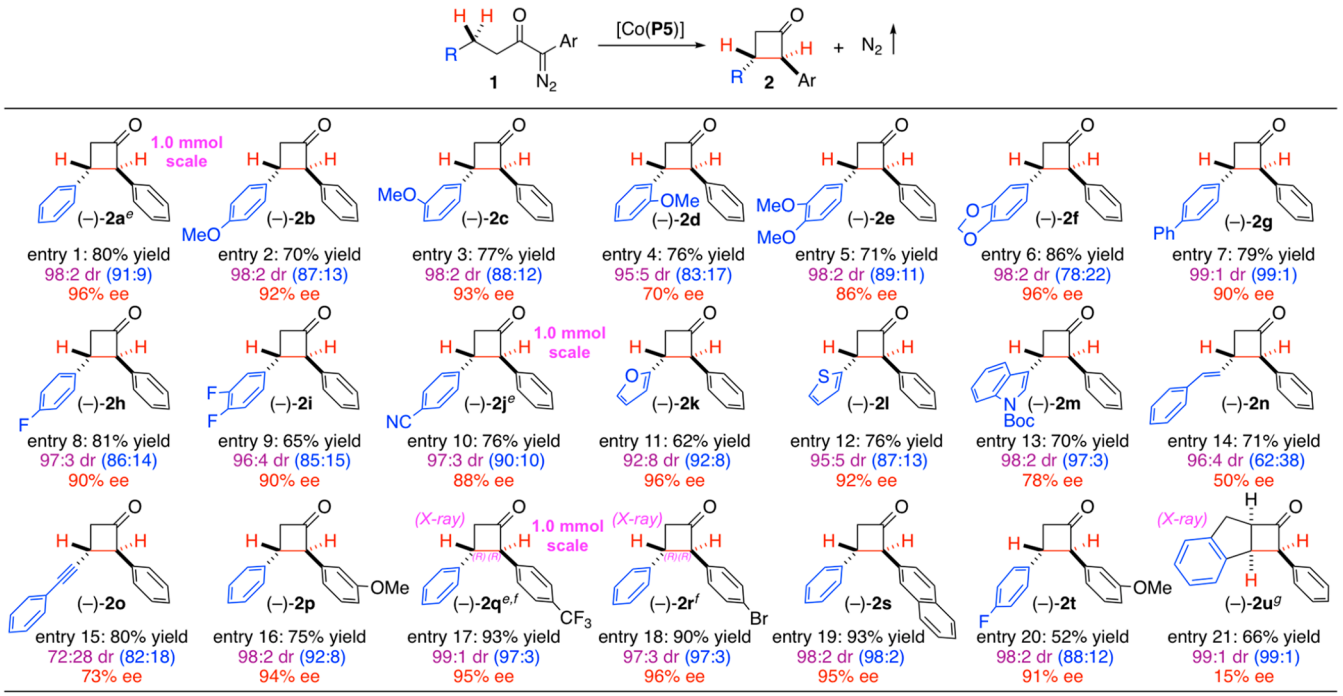
Table 1. Asymmetric Synthesis of Cyclobutanones by Co(II)-Catalyzed 1,4-C−H Alkylation of α-Diazoketones[a,b,c,d]



[a]Carried out with **1** (0.10 mmol) and [Co(**P5**)] (2 mol %) in TBME (0.5 mL) at 40 °C for 12 h. [b]Isolated yield. [c]Diastereomeric ratio (dr) determined by ^{1}H NMR analysis: *trans*-enriched products after purification by silica gel column chromatography due to isomerization; value in parathesis determined from reaction mixture before purification. [d]Enantiomeric excess (ee) of *trans*-diastereomer determined by chiral HPLC after purification. [e]Reaction performed in 1.0 mmol scale. [f]Absolute configuration determined by X-ray crystallography. [g]Relative configuration determined by X-ray crystallography.

RESULTS AND DISCUSSION

Catalyst Development. At the outset of this research project, 1-diazo-1,4-diphenylbutan-2-one (**1a**) was used as the model substrate to examine the feasibility of the proposed catalytic process for 1,4-C−H alkylation (Scheme 2). Simple achiral metalloradical catalyst [Co(TPP)] (TPP = 5,10,15,20-tetraphenylporphyrin) was shown to be incapable of activating **1a** for the intramolecular C−H alkylation reaction, failing to generate any cyclobutanone product. Instead, diazoketone **1a** was thermally decomposed to the carboxylic acid derivative via Wolff rearrangement, followed by nucleophilic reaction of the corresponding ketene intermediate with water. Excitingly, when the achiral amidoporphyrin catalyst [Co(**P1**)] (**P1** = 3,5-Di^{t}Bu-IbuPhyrin)[15] was used, it could productively catalyze the C−H alkylation reaction to deliver the desired product 2,3-diphenylcyclobutan-1-one (**2a**) in 54% yield with 40% de. The dramatic difference in reactivity between [Co(**P1**)] and [Co(TPP)] might be attributed to rate acceleration through the potential hydrogen bonding interaction between amide units of the porphyrin and the carbonyl group of the α-diazoketone. Employment of first-generation chiral metalloradical catalyst [Co(**P2**)] (**P2** = 3,5-Di^{t}Bu-ChenPhyrin)[7a] enabled asymmetric induction in the 1,4-C−H alkylation reaction, affording cyclobutanone **2a** with moderate enantioselectivity (46% ee) without significantly affecting the product yield (50%) and diastereoselectivity (52% de). When second-generation chiral metalloradical catalyst [Co(**P3**)] (**P3** = 3,5-Di^{t}Bu-TaoPhyrin) bearing chiral amide units with ester moieties was used for the catalytic reaction,[16] it led to the increase in both product yield (71%) and diastereoselectivity (86% de) but the decrease in enantioselectivity (15% ee). When switching to new-generation C_6-bridged metalloradical catalyst [Co(**P4**)] (**P4** = 3,5-Di^{t}Bu-Hu(C_6)Phyrin) featuring more rigid cavity-like environments,[16] dramatic improvements in both diastereoselectivity (94% de) and enantioselectivity (78% ee) were observed even if in relatively lower product yield (61%). Subsequent use of analogous catalyst [Co(**P5**)] (**P5** = 2,6-DiMeO-Hu(C_6)Phyrin),[17] which bears 2,6-dimethoxyphenyl instead of 3,5-di-*tert*-butylphenyl groups as the 5,15-diaryl substituents, further improvements in enantioselectivity (96% ee) as well as yield (80%) were achieved without significantly affecting the diastereoselectivity (82% de). These results demonstrate that the rigidification of ligand environment of chiral metalloradical catalyst [Co(D_2-Por*)] plays an important role in achieving both high reactivity and stereoselectivity for the 1,4-C−H alkylation process. It should be emphasized that the diastereomeric mixtures of the resulting cyclobutanone **2a** from all the catalytic reactions were isomerized to *trans*-enriched **2a** with 96% de after purification by column chromatography on silica gel as a result of the relative acidity of the tertiary α-C−H bond, regardless the original diastereoselectivities before purification.

Substrate Scope. Under the optimized conditions, the substrate scope of the [Co(**P5**)]-catalyzed intramolecular 1,4-C−H alkylation was evaluated with α-aryldiazoketones **1** containing different types of C−H bonds (Table 1). Like the parent **1a**, 1,4-diaryl-α-diazoketone derivatives containing 4-aryl substituents with various steric and electronic properties at different positions, including 4-OMe (**1b**), 3-OMe (**1c**), 2-OMe (**1d**), 3,4-di-OMe (**1e**), 1′,3′-dioxolane-3,4-fused (**1f**), 4-Ph (**1g**), 4-F (**1h**), 3,4-di-F (**1i**), and 4-CN (**1j**), could be efficiently alkylated by [Co(**P5**)] at the benzylic C−H bonds,

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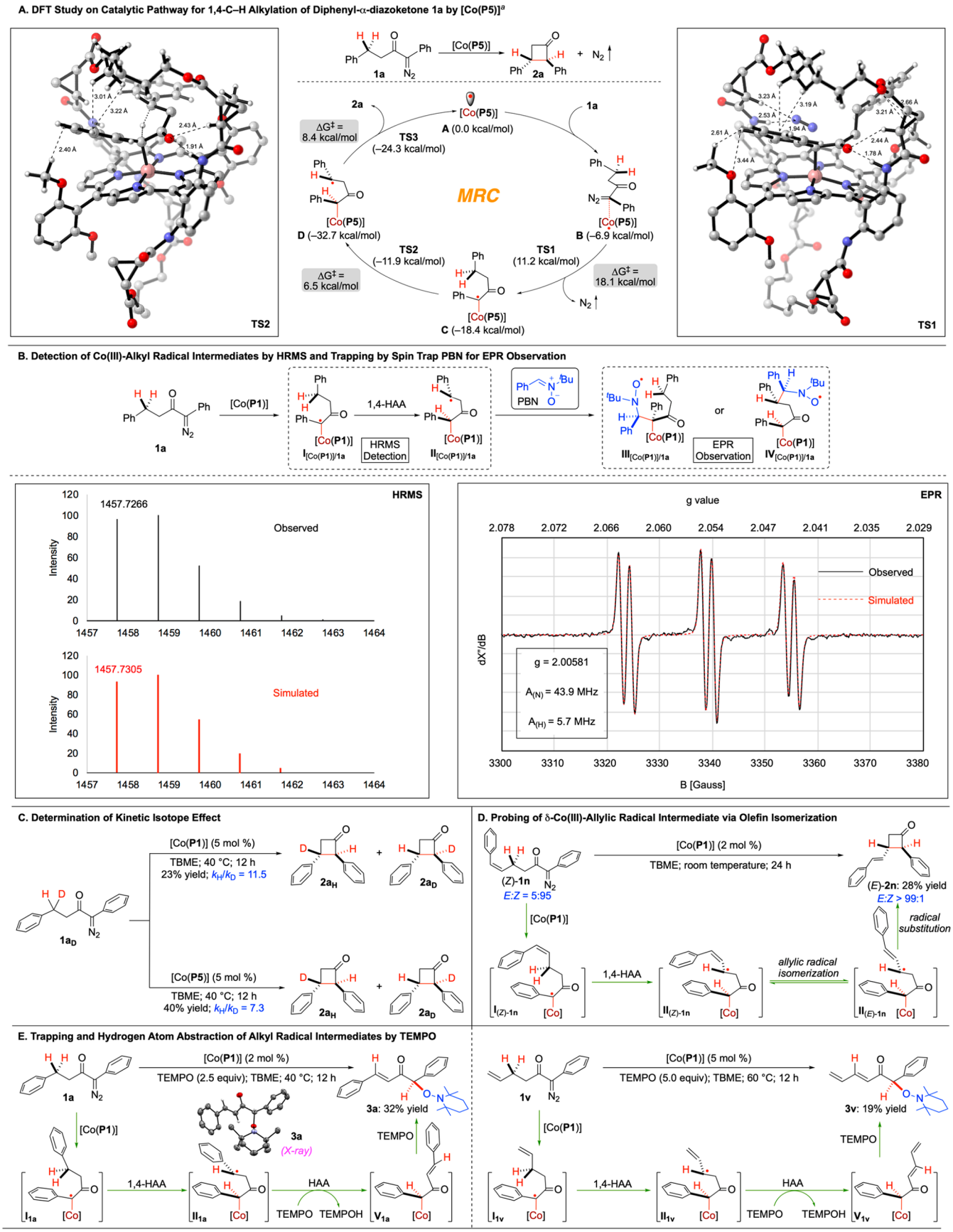
Scheme 3. Mechanistic Studies on Co(II)-Catalyzed 1,4-C−H Alkylation of α-Aryldiazoketones



[a]Free energy profile of the [Co(P5)]-catalyzed 1,4-C−H alkylation. Density functional theory calculations were performed at SMD(diisopropylether)-BP86-D3(BJ)/def2TZVPP//BP86-D3(BJ)/def2SVP level of theory.

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delivering the corresponding cyclobutanones **2b**−**2j** in good yields with high enantioselectivities (Table 1; entries 2−10). The Co(II)-catalyzed 1,4-C−H alkylation was shown to be compatible with substrates containing heteroarenes, such as furan (**1k**), thiophene (**1l**) and indole (**1m**), allowing for stereoselective construction of β-heteroarylcyclobutanones **2k**−**2m** in similarly good yields with the same high enantioselectivities (Table 1; entries 11−13). Furthermore, the Co(II)-based catalytic system could chemoselectively alkylate allylic C−H bonds without affecting the typically more reactive C=C π bonds as demonstrated by the productive formation of β-alkenylcyclobutanone **2n** from the reaction of 4-alkenyl-substituted diazoketone (*Z*)-**1n** in good yield albeit with lower enantioselectivity (Table 1; entry 14). It was noted that the olefin configuration was completely isomerized from (*Z*) to (*E*) during the catalytic process (see Scheme 3D for detailed discussion). Likewise, propargylic C−H bonds could also be chemoselectively alkylated by [Co(**P5**)] without reacting with the C≡C π bonds, as exemplified by the reaction of 4-alkynyl-substituted diazoketone **1o** to generate β-alkynylcyclobutanone **2o** in good yield with better enantioselectivity (Table 1; entry 15). In addition to the substrates with different 4-aryl substituents, the Co(II)-based metalloradical system was shown to be applicable to α-diazoketones containing 1-aryl substituents with various steric and electronic properties at different positions. For example, catalytic 1,4-C−H alkylation reactions of 1-aryl-4-phenyl-α-diazoketones, such as those bearing 3-OMe (**1p**), 4-CF_3 (**1q**), and 4-Br (**1r**) phenyl groups as well as 2-naphthyl group (**1s**), proceeded smoothly to afford the corresponding cyclobutanones **2p**−**2s** in good to high yields with excellent enantioselectivities (Table 1; entries 16−19). 1,4-Diaryl-α-diazoketones containing both 1- and 4-aryl substituents were found to work equally well as shown with the successful reaction of α-diazoketone **1t** for formation of the desired α,β-bisarylcyclobutanone **2t** with excellent level of enantioselectivity despite in moderate yield (Table 1; entry 20). Furthermore, the Co(II)-based catalytic system could be also applicable to cyclic substrates such as 2-indane-derived α-diazoketone **1u**, resulting in asymmetric desymmetrization of the two benzylic C−H sites in the indane ring to deliver cyclobutanone **2u** (Table 1; entry 21). It is remarkable that the strained tricyclic structure with fused 4-/5-membered rings could be constructed through catalytic 1,4-C−H alkylation in good yield despite with low enantioselectivity. A new Co(II)-metalloradical catalyst supported by a different type of D_2-symmetric chiral amidoporphyrin ligand would likely be needed in order to achieve high enantioselectivity for the asymmetric desymmetrization 1,4-C−H alkylation process. Finally, [Co(**P5**)] was found to be ineffective for 1,4-alkylation of nonbenzylic C−H bonds due to the competition from predominant 1,5-C−H alkylation. However, preliminary results from the catalytic reaction of 1-diazo-1,7-diphenylheptane-2-one with C−H bonds at different positions indicated that site-selective 1,4- over 1,5-C−H alkylation could be potentially achieved through fine-tuning of the D_2-symmetric chiral amidoporphyrin as the supporting ligand for Co(II)-metalloradical catalyst (see Scheme S1 in Supporting Information for the details). As aforementioned, the diastereomeric mixtures of the resulting cyclobutanones **2**, regardless the original diastereoselectivities from the catalytic reactions, were all further enriched to give *trans*-dominant products with excellent diastereoselectivities after purification by column chromatography on silica gel (Table 1), which was realized by isomerization as a result of the relative acidity of the tertiary α-C−H bonds. The only exception was observed for product **2o**, the diastereoselectivity of which was decreased after the purification (Table 1; entry 15), which is presumably a result of the less steric hindrance of the alkyne group. It is worth mentioning that the Co(II)-based catalytic process for the synthesis of cyclobutanone derivatives could be readily scaled up under the same condition as exemplified by the stereoselective syntheses of optically active cyclobutanones **2a**, **2j** and **2q** on 1.0 mmol scale in similarly good yields with the same level of high enantioselectivities (Table 1; entries 1, 10 and 17).

Mechanistic Studies. To gain insights into this metalloradical process, combined computational and experimental studies were conducted to explore the proposed stepwise radical mechanism for the Co(II)-catalyzed 1,4-C−H alkylation (Scheme 1). First, density functional theory (DFT) calculations were performed to elucidate the catalytic pathway for 1,4-C−H alkylation reaction of α-aryldiazoketone **1a** with the use of the actual catalyst [Co(**P5**)] (Scheme 3A; see Supporting Information for details). The computational study reveals the initial formation of intermediate **B** between diazo **1a** and catalyst [Co(**P5**)] through a network of noncovalent attractions, including multiple H-bonds and π-interactions. This complexation process, which is exergonic by 6.9 kcal/mol, places the substrate underneath the bridge of the catalyst and positions the α-carbon atom of diazo **1a** in a close proximity to the Co center of [Co(**P5**)] (C---Co: ∼ 2.70 Å) for further interaction. Upon metalloradical activation (MRA) by [Co(**P5**)], the bound **1a** undergoes the extrusion of dinitrogen to generate α-Co(III)-alkyl radical **C**. The metalloradical activation step, which is exergonic by 11.5 kcal/mol, is found to be associated with a relatively high but accessible activation barrier (**TS1**: $\Delta G^{\ddagger}$ = 18.1 kcal/mol). Subsequent 1,4-HAA of intermediate **C**, which is exergonic by 14.3 kcal/mol, gives rise to the corresponding δ-Co(III)-alkyl radical intermediate **D** with a relatively low activation barrier (**TS2**: $\Delta G^{\ddagger}$ = 6.5 kcal/mol). Such a low barrier for 1,4-HAA revealed by the DFT computation, which is uncommon for free radical processes,[18] may be attributed to the presence of the multiple noncovalent interactions that stabilize transition state **TS2**. As illustrated by the computed model of **TS2** (Scheme 3A), these cooperative noncovalent attractive interactions orient the reacting substrate within the catalyst cavity in proximity with proper conformation to facilitate the 1,4-HAA. According to the DFT calculations, the final step of *4-exo-tet* cyclization of alkyl radical **D** via intramolecular radical substitution also has a relatively low activation barrier (**TS3**: $\Delta G^{\ddagger}$ = 8.4 kcal/mol), leading to the formation of cyclobutanone **2a** while regenerating catalyst [Co(**P5**)].

To experimentally detect α-Co(III)-alkyl radical **I** and δ-Co(III)-alkyl radical **II**, the reaction mixture of α-aryldiazoketone **1a** with catalyst [Co(**P1**)] was analyzed by high-resolution mass spectrometry (HRMS) with electrospray ionization (ESI) in the absence of any additives as electron carriers (Scheme 3B). The obtained spectrum clearly reveals a signal corresponding to [(**P1**)Co−C(C_6H_5)(C(O)-

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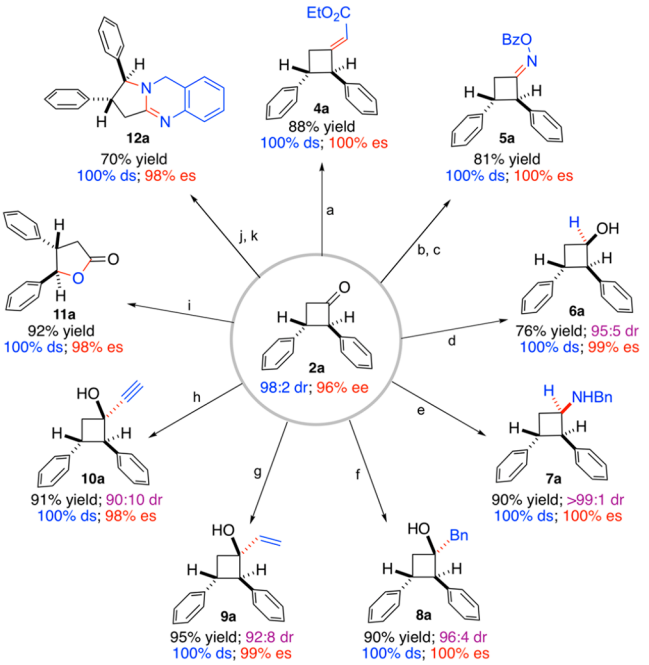
$CH_2CH_2C_6H_5)]^+$ (m/z = 1457.7266), which resulted from neutral α-Co(III)-alkyl radical intermediate $\mathbf{I}_{[Co(P1)]/1a}$ or δ-Co(III)-alkyl radical intermediate $\mathbf{II}_{[Co(P1)]/1a}$ by the loss of one electron. Both the exact mass and the pattern of isotope distribution determined by ESI-HRMS matches almost perfectly with those calculated from the formula $[C_{92}H_{102}CoN_8O_5]^+$ (see Supporting Information for details). In addition to the HRMS detection, we made multiple attempts to observe $\mathbf{I}_{[Co(P1)]/1a}$ and $\mathbf{II}_{[Co(P1)]/1a}$ by electron paramagnetic resonance (EPR) without success. This negative outcome of EPR observation was attributed to the fleeting nature of the alkyl radical intermediates as a result of facile 1,4-HAA and RS steps, as revealed from DFT calculations. Accordingly, the common spin trap phenyl *N*-*tert*-butyl-α-phenylnitrone (PBN) was employed to trap $\mathbf{I}_{[Co(P1)]/1a}$ or $\mathbf{II}_{[Co(P1)]/1a}$, which resulted in the generation of radicals $\mathbf{III}_{[Co(P1)]/1a}$ or $\mathbf{IV}_{[Co(P1)]/1a}$ that could be successfully observed by EPR at room temperature (Scheme 3B; see Supporting Information for details). The observed triplet of doublet signals in the isotropic EPR spectrum could be fittingly simulated on the basis of hyperfine couplings by ^{14}N (I = 1) and ^{1}H (I = 1/2): g = 2.00581; $A_{(N)}$ = 43.9 MHz; $A_{(H)}$ = 5.7 MHz.

To further study the 1,4-HAA step in the catalytic process, monodeuterated diazo $\mathbf{1a_D}$ was prepared as the substrate for the study of kinetic isotopic effect (KIE) using both achiral catalyst [Co(**P1**)] and chiral catalyst [Co(**P5**)] (Scheme 3C). The KIE values for the catalytic reaction of diazo $\mathbf{1a_D}$ by [Co(**P1**)] and [Co(**P5**)] were determined to be 11.5 and 7.3, respectively. These large values of primary KIE are in good agreement with the proposed step of homolytic C−H bond cleavage via intramolecular H-atom abstraction by α-Co(III)-alkyl radical intermediate **I**. To further probe the existence of δ-Co(III)-alkyl radical intermediate **II**, (*Z*)-**1n** was employed as the substrate for 1,4-C−H alkylation reaction using [Co(**P1**)] as the catalyst (Scheme 3D). Like the catalytic reaction by [Co(**P5**)] (Table 1; entry 14), it was found that (*E*)-**2n** was generated as the only product, indicating isomerization of the olefin configuration during the catalytic process. The formation of (*E*)-**2n** from (*Z*)-**1n** implies the involvement of δ-Co(III)-allylic radical $\mathbf{II}_{(E)\text{-}1n}$, which could be generated through isomerization of δ-Co(III)-allylic radical $\mathbf{II}_{(Z)\text{-}1n}$. To directly trap the alkyl radical intermediate, the catalytic reaction of **1a** using [Co(**P1**)] as the catalyst was conducted in the presence of TEMPO (Scheme 3E). Interestingly, TEMPO-trapping product **3a** was isolated in 32% yield, the structure of which was confirmed by X-ray crystallography. Formation of **3a** further implies the initial generation of α-Co(III)-alkyl radical $\mathbf{I}_{1a}$ by MRA, followed by 1,4-HAA to deliver δ-Co(III)-alkyl radical $\mathbf{II}_{1a}$ in the catalytic reaction. Instead of radical recombination with TEMPO, it is presumed to be more favorable for intermediate $\mathbf{II}_{1a}$ to undergo HAA by TEMPO, furnishing Co(III)-alkyl intermediate $\mathbf{V}_{1a}$ with the extended conjugation. Subsequent radical substitution with another molecule of TEMPO delivered the TEMPO-trapping product **3a**. In a similar pathway, the catalytic reaction of allyl diazoketone **1v** by [Co(**P1**)] in the presence of TEMPO could give TEMPO trapping product **3v**, indicating the involvement of the corresponding radical intermediates $\mathbf{I}_{1v}$, $\mathbf{II}_{1v}$ and $\mathbf{V}_{1v}$. Furthermore, catalytic reactions of allyl diazoketone bearing a cyclopropyl ring as radical-clock substrate were performed with [Co(**P5**)] in both absence and presence of TEMPO to probe the lifetime of the corresponding δ-Co(III)-alkyl radical intermediate. Since there was no evidence for formation of ring-opening product in both reactions, it was concluded that the C−C and related bond formation were faster than the ring-opening of the cyclopropylcarbinyl radical within the cavity-like ligand environment of the catalyst (see Supporting Information for details).

Synthetic Applications. Considering that the resulting enantioenriched cyclobutanones contain both versatile carbonyl group and strained four-membered structure, they may serve as useful intermediates for stereoselective organic synthesis (Scheme 4). To demonstrate the synthetic utility of this

Scheme 4. Synthetic Transformations of Resulting Chiral Cyclobutanones from Co(II)-Catalyzed 1,4-C−H Alkylation[a]



[a](a) Triethyl Phosphonoacetate (1.5 equiv); Sodium Hydride (1.2 equiv); THF; RT; 12 h. (b) Hydroxylamine Hydrochloride (2.0 equiv); Pyridine; RT; 2 h. (c) Benzoyl Chloride (1.5 equiv); Triethylamine (2.0 equiv); DCM; 0 °C; 6 h. (d) Sodium Borohydride (1.0 equiv); MeOH; −78 °C; 10 h. (e) Benzylamine (1.1 equiv); Sodium Triacetoxyborohydride (2.0 equiv); DCM; RT; 12 h. (f) Benzylmagnesium Chloride (1.5 equiv); THF; 0 °C; 1 h. (g) Vinylmagnesium Bromide (1.5 equiv); THF; 0 °C; 1 h. (h) Ethynylmagnesium Bromide (1.5 equiv); THF; 0 °C; 1 h. (i) *m*-CPBA; DCM; 0 °C; 2 h. (j) *o*-Aminobenzylamine (1.1 equiv); $CHCl_3$; 60 °C; 9 h. (k) NCS (1.5 equiv); DCM; 0 °C; 2 h.

methodology, we carried out a series of synthetic transformations using enantioenriched cyclobutanone **2a** (96% ee) as the model reactant. For example, cyclobutanone **2a** could undergo efficient Horner-Wadsworth-Emmons reaction to provide the corresponding chiral methylenecyclobutane **4a** in high yield without the loss of either diastereopurity or enantiopurity. Cyclobutanone **2a** could also be stereospecifically converted to the corresponding *O*-benzoyl oxime **5a**, which is known to undergo various ring-opening transformations.[19] In addition, **2a** could undergo both efficient reduction and reductive amination, allowing for the production of chiral cyclobutanol **6a** and cyclobutanamine **7a**, respectively, with excellent diastereoselectivities. Moreover, the ketone functionality in cyclobutanone **2a** could undergo nucleophilic

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addition with Grignard reagents such as benzylmagnesium chloride, vinylmagnesium bromide, and ethynylmagnesium bromide to provide corresponding cyclobutanols **8a**, **9a**, and **10a** bearing a newly-formed quaternary stereogenic center in excellent yields with effective control of diastereoselectivities. It is worth mentioning that tertiary cyclobutanols such as **8a**, **9a**, and **10a** can be potentially employed for downstream functionalization via C−C bond cleavage.[20] In view of the wide applications of the chiral γ-lactone scaffold,[21] it was shown that γ-lactone **11a** could be efficiently generated from cyclobutanone **2a** through Baeyer-Villiger oxidation with the retention of the original stereochemical purity. Gratifyingly, chiral dihydroquinazoline **12a**, as a family of heterocycles with interesting biological activities,[22] could be synthesized from the reaction of **2a** with *o*-aminobenzylamine through simple two-step transformation.[23]

CONCLUSIONS

In summary, we have demonstrated the first catalytic system for asymmetric radical 1,4-C−H alkylation via Co(II)-based MRC that involves the typically challenging 1,4-hydrogen atom abstraction. The key to the successful development is the judicious modulation of D_2-symmetric chiral amidoporphyrin ligand to adopt desired steric, electronic and chiral environments around the Co(II)-metalloradical center that maximize a network of noncovalent attractive interactions in catalytic intermediates. With the bridged D_2-symmetric chiral amidoporphyrin 2,6-DiMeO-Hu(C_6)Phyrin as the optimal supporting ligand, the Co(II)-based metalloradical system, which operates under mild conditions, can catalyze asymmetric 1,4-C−H alkylation of α-aryldiazoketones with varied electronic and steric properties to construct chiral α,β-disubstituted cyclobutanones in good yields with high diastereoselectivities and enantioselectivities. The combined computational and experimental studies have shed light on the working details of this new catalytic process that proceeds through a stepwise radical mechanism, which is fundamentally different from the concerted C−H insertion by the existing catalytic systems involving metallocarbenes. As showcased with several enantiospecific transformations to other types of cyclic structures from the resulting enantioenriched α,β-disubstituted cyclobutanones, this Co(II)-based metalloradical system for asymmetric 1,4-C−H alkylation should find broad applications in organic synthesis. We envision that catalytic radical processes incorporating 1,4-H-atom abstraction as the key step may offer a general strategy for asymmetric construction of highly strained four-membered cyclic structures.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.1c04968.

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

Accession Codes

CCDC 2083314−2083317 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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