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Enantioselective radical process for synthesis of chiral indolines by metalloradical alkylation of diverse C(sp^3)–H bonds†

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A new C–C bond formation strategy based on enantioselective radical alkylation of C(sp^3)–H bonds *via* Co(II)-based metalloradical catalysis has been demonstrated for stereoselective synthesis of chiral indolines. The Co(II)-based system enables activation of aryldiazomethanes as radical precursors at room temperature for enantioselective intramolecular radical alkylation of broad types of C–H bonds, constructing 2-substituted indolines in high yields with excellent enantioselectivities. In addition to chemoselectivity and regioselectivity, this Co(II)-catalyzed alkylation features tolerance to functional groups and compatibility with heteroaryl substrates. Detailed mechanistic studies provide insight into the underlying stepwise radical pathway.

Introduction

Recent years have witnessed intense research efforts in exploring the unique features of radical reactions for organic synthesis.[1] Among the diverse types of radical reactions, hydrogen atom abstraction (HAA) has been recognized as a general pathway to activate C(sp^3)–H bonds, offering a potential approach for C–C bond formation *via* direct radical C–H alkylation.[2] In addition to the prerequisite for controlled generation of the incoming radicals, development of HAA-based radical C–H alkylation, however, faces formidable challenges associated with governing the reactivity and selectivity of the outgoing alkyl radicals for ensuing C–C bond formation. In particular, control of enantioselectivity of radical reactions is typically difficult.[1,2] Among recent developments,[3] metalloradical catalysis (MRC), which involves the use of metal-centered radicals for catalytic generation of metal-stabilized organic radicals while controlling their radical reactions, has emerged as a conceptually new approach for the development of stereoselective radical processes.[4,5] As stable metalloradicals, Co(II) complexes of D_2-symmetric chiral amidoporphyrins [Co(D_2-Por*)] exhibit the capability of homolytically activating diazo compounds as radical precursors to generate α-Co(III)-alkyl radicals.[6] These Co-stabilized C-centered radicals can serve as key catalytic intermediates for asymmetric radical transformations.[7] Recently, Co(II)-based MRC was further extended to the use of donor-substituted diazo compounds such as aryldiazomethanes as radical precursors.[8] Upon activation, the resulting α-Co(III)-benzyl radicals could undergo radical addition to C=C bonds and radical substitution for stereoselective radical cyclopropanation.[8a] Besides radical addition, we were interested in exploring the potential ability of α-Co(III)-benzyl radicals for HAA that might lead to radical alkylation of C–H bonds. Particularly, we were attracted to aryldiazomethane **1′** with *ortho*-amino functionality and hypothesized that the corresponding α-Co(III)-benzyl radical intermediate **A** would favor intramolecular HAA from the C–H bonds at the distal 5-position to form ε-Co(III)-aminoalkyl radical **B**, where the C-centered radical would be stabilized by the lone pair of the adjacent nitrogen (Scheme 1). If the α-aminoalkyl radical in **B** could proceed 5-*exo*-*tet* radical cyclization at the α-carbon for C–C bond formation in an asymmetric fashion, it would lead to a new catalytic system for enantioselective radical C–H alkylation to construct chiral 2-substituted indolines, which exist ubiquitously in natural and synthetic compounds (Fig. S1 in ESI†).[9]

Tremendous efforts have been devoted to asymmetric synthesis of 2-substituted indolines due to their biological importance.[10] Among others,[11] existing methods have explored strategies that are based on asymmetric hydrogenation of C2=C3 bond,[11a,b] asymmetric alkylation at C2 position,[11c] asymmetric formation of C3–C3a bond,[11d,e] as well as asymmetric formation of N1–C7a[11f–h] and N1–C2 bonds.[11i] However, stereoselective construction of chiral 2-substituted indolines that is based on asymmetric formation of C2–C3 bond *via* C–H alkylation has been less developed.[12] This underdevelopment may be attributed to the inherent challenge for enantioselective formation of C–C bonds between two sp^3-carbons. To date, there is no previous report on asymmetric construction of 2-substituted indolines through C2(sp^3)–C3(sp^3) bond formation

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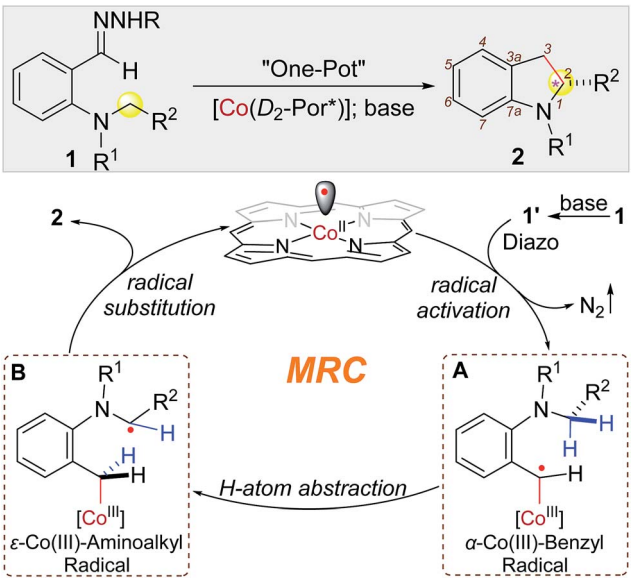


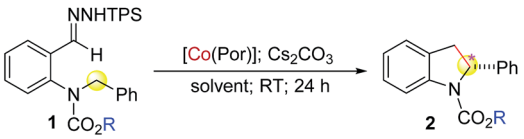
Scheme 1 Working proposal for construction of 2-substituted indolines by radical C–H alkylation *via* Co(II)-MRC.

via stereoselective C(sp^3)–H alkylation using donor-type diazo compounds. As a new synthetic application of Co(II)-MRC, we herein report the development of the first catalytic system for asymmetric synthesis of 2-substituted indolines *via* enantioselective radical C–H alkylation of aryldiazomethanes, which can be generated *in situ* from readily accessible aryl aldehyde-derived hydrazone precursors. Through the design of a new D_2-symmetric chiral amidoporphyrin, the Co(II)-catalyzed process can alkylate diverse types of C–H bonds at room temperature to form chiral 2-substituted indolines.

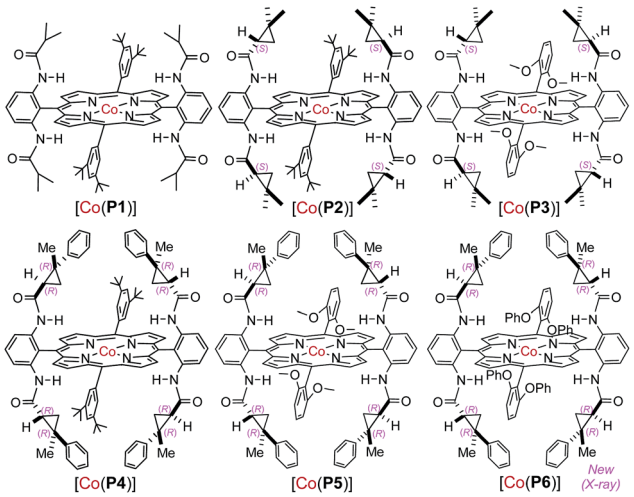
Results and discussion

At the outset, *o*-aminobenzaldehyde-derived hydrazone **1a** was selected to examine the feasibility of Co(II)-catalyzed radical C–H alkylation (Table 1). It was found that Co(II) complex of D_{2h}-symmetric achiral amidoporphyrin [Co(**P1**)] (**P1** = 3,5-Di^{t}Bu-IbuPhyrin)[13] was an effective metalloradical catalyst, delivering the desired 2-phenylindoline **2a** in 81% yield even at room temperature (entry 1). The high yield implies that the *in situ* generation of the corresponding aryldiazomethane from **1a** was facile and properly matched with the rate of its activation by the catalyst toward the C–H alkylation. To achieve enantioselectivity, the use of the first-generation chiral catalyst [Co(**P2**)] (**P2** = 3,5-Di^{t}Bu-ChenPhyrin)[7e] resulted in **2a** in a similar yield with a low but significant enantioselectivity (entry 2). The asymmetric induction was improved without affecting the yield when the more sterically demanding catalyst [Co(**P3**)] (**P3** = 2,6-DiMeO-ChenPhyrin) was used (entry 3). This ligand buttressing effect prompted us to evaluate the second-generation catalyst [Co(**P4**)] (**P4** = 3,5-Di^{t}Bu-QingPhyrin).[7b] Indeed, both the reactivity and enantioselectivity were significantly enhanced (entry 4). In a similar trend, when sterically more encumbered [Co(**P5**)] (**P5** = 2,6-DiMeO-QingPhyrin) was used, improvement in enantioselectivity continued (entry 5). To amplify such effect, we synthesized the new catalyst [Co(**P6**)] (**P6** = 2,6-DiPhO-QingPhyrin) by replacing the methoxy groups in **P5** with phenoxy groups, which could catalyze **2a** formation in 82% yield with 66% ee (entry 6). Using [Co(**P6**)], we then examined the effect of *N*-substituents in substrate **1** on the reaction. Change from *t*-butyl (**1a**) to ethyl (**1b**) to methyl (**1c**) carbamates led to a successive increase in both yield and ee, achieving almost quantitative yield and 86% ee in the case of **1c** (entries 6–8). This outcome might be attributed to the potential hydrogen-bonding

Table 1 Optimization of Co(II)-based catalytic system for enantioselective radical C–H alkylation of aryldiazomethanes[a]



Entry	R	Catalyst	Solvent	Yield[b] (%)	ee[c] (%)
1	*t*-Bu (**1a**)	[Co(**P1**)]	Toluene	81	–
2	*t*-Bu (**1a**)	[Co(**P2**)]	Toluene	74	10
3	*t*-Bu (**1a**)	[Co(**P3**)]	Toluene	75	19
4	*t*-Bu (**1a**)	[Co(**P4**)]	Toluene	92	38
5	*t*-Bu (**1a**)	[Co(**P5**)]	Toluene	90	42
6	*t*-Bu (**1a**)	[Co(**P6**)]	Toluene	82	66
7	Et (**1b**)	[Co(**P6**)]	Toluene	92	86
8	Me (**1c**)	[Co(**P6**)]	Toluene	99	86
9	Me (**1c**)	[Co(**P6**)]	Benzene	99	86
10	Me (**1c**)	[Co(**P6**)]	Tetrahydrofuran	78	83
11	Me (**1c**)	[Co(**P6**)]	Dimethoxyethane	95	88
12	**Me (1c)**	**[Co(P6)]**	**Methanol**	**92**	**94**
13	Me (**1c**)	[Co(**P6**)]	Diethyl ether	98	82



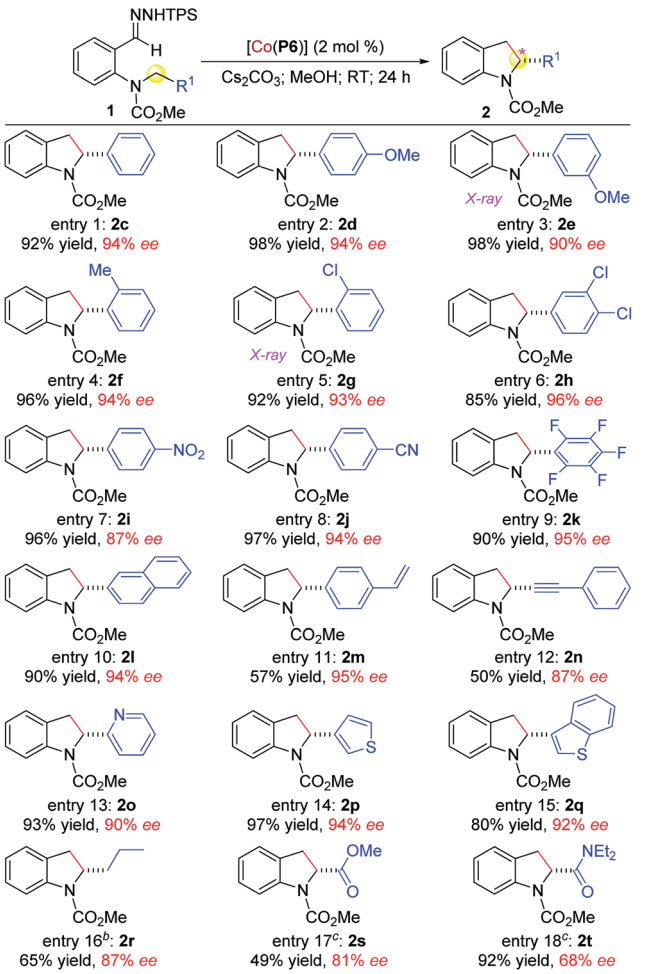
[a] Carried out with **1** (0.1 mmol) in the presence of Cs_2CO_3 (2.0 equiv.) by [Co(**Por**)] (2 mol%) in solvent (1.0 mL); TPS = 2,4,6-triisopropylphenyl sulfonyl. [b] Isolated yields. [c] Determined by chiral HPLC.

interaction between the carbonyl group of the carbamate and the amido group of the catalyst, which strengthens upon the decrease in sterics (Fig. S2†). Further investigation revealed that both polar and non-polar solvents were suitable (entries 8–13). The solvent of choice was methanol, affording 2-phenylindoline **2c** in 92% yield with 94% ee (entry 12; see Table S1† for the effect of different sulfonyl groups).

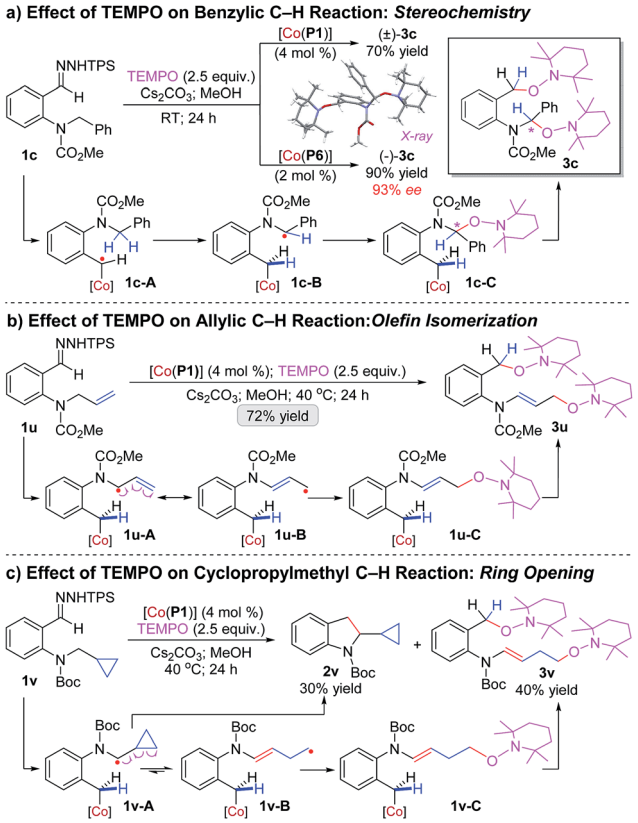
Under the optimized conditions, the scope of [Co(**P6**)]-catalyzed radical alkylation was evaluated by employing different C–H substrates (Table 2). As demonstrated with substrates **1c–1k**, benzylic C–H bonds having varied electronic and steric properties could be effectively alkylated at room temperature in a highly enantioselective fashion, affording chiral 2-arylindolines **2c–2k** in excellent yields (entries 1–9). The absolute configurations of **2e** and **2g** were established by X-ray crystal structural analysis as (R) (see ESI†). It is noteworthy to mention that even the highly electron-deficient pentafluorobenzylic C–H bond in **1k** could successfully undergo radical alkylation, forming **2k** in 90% yield with 95% ee (entry 9). The system could also alkylate C–H bonds adjacent to other arenes as shown with the 2-naphthyl-based substrate **1l** (entry 10). Besides $-NO_2$ and –CN functionalities (entries 7 and 8), the alkylation tolerated both alkenyl and alkynyl groups, as demonstrated by the stereoselective formation of **2m** and **2n** without complications from potential reactions with the C=C and C≡C bonds, respectively (entries 11 and 12). Notably, this system was equally effective for alkylation of C–H bonds next to heteroarenes, such as pyridine (**1o**), thiophene (**1p**), and benzothiophene (**1q**), providing 2-heteroarylindolines **2o–2q** in high yields and enantioselectivities (entries 13–15). Given that both heteroarene and indoline are prevalent structural elements in bioactive natural and synthetic compounds, the access of these linked biheterocyclic compounds in high enantiopurity may find applications in pharmaceutical research and development. Furthermore, non-activated C–H bonds could also be alkylated, as exemplified by the regioselective 1,5-alkylation of **1r**, forming 2-propylindoline (**2r**) in 65% yield with 87% ee although 60 °C was needed (entry 16). The alkylation was further highlighted by its applicability to even C–H bonds that are directly attached to electron-withdrawing groups. For example, electron-poor C–H bonds that are adjacent to ester (**1s**) and amide (**1t**) groups were smoothly alkylated at 40 °C to furnish the 2-ester (**2s**)- and 2-amido (**2t**)-indolines in varied yields and enantioselectivities (entries 17 and 18). These results manifested the low sensitivity of the Co(II)-based alkylation to the electronic properties of C–H bonds, which are consistent with its underlying radical mechanism.

To gain insight into the underlying mechanism of this Co(II)-catalyzed C–H alkylation, a set of mechanistic experiments were conducted (Scheme 2). First, the effect of TEMPO was examined. Addition of TEMPO to the reaction of benzyl C–H substrate **1c** by achiral catalyst [Co(**P1**)] resulted in no formation of C–H alkylation product **2c**. Instead, compound (±)-**3c** was isolated in 70% yield, whose structure was confirmed by X-ray analysis to contain two TEMPO units at the 1- and 5-positions (Scheme 2a). The formation of (±)-**3c** is indicative of the existence of the initial α-Co(III)-benzyl radical (**1c-A**) as well as the resulting ε-Co(III)-aminoalkyl radical (**1c-B**) from 1,5-HAA, which was presumably capped subsequently by TEMPO at the ε-position through radical recombination to generate intermediate **1c-C** and then followed by radical substitution with second TEMPO at the α-position to break the weak Co(III)–C bond for final production of (±)-**3c**. To gain information on stereochemistry, the same reaction was performed with chiral catalyst [Co(**P6**)] (Scheme 2a). The same bis-TEMPO-capped compound (−)-**3c** was generated, but in a much higher yield of 90% and, remarkably, with 93% ee. The fact that the enantioselectivity for the C–O bond formation (93% ee) of the TEMPO-capped product (−)-**3c** was almost identical to the one observed for the C–C bond formation (94% ee) of the C–H alkylation product **2c** in the absence of TEMPO (Table 2: entry 1) implies that the prochiral α-aminoalkyl radical in **1c-B** was confined inside the chiral pocket of [Co(**P6**)] to adapt a stable, well-defined configuration. In addition, the resulting Co(III)-supported alkyl radical intermediates from the reaction of **1c** by [Co(**P1**)] in the absence

Table 2 [Co(**P6**)]-catalyzed enantioselective radical C–H alkylation for construction of chiral 2-substituted indolines[a]



[a] Carried out with **1** (0.1 mmol) in the presence of Cs_2CO_3 (2.0 equiv.) in MeOH (1.0 mL); isolated yields; ee was determined by chiral HPLC. [b] At 60 °C. [c] At 40 °C.



Scheme 2 Mechanistic studies on Co(II)-catalyzed intramolecular radical C–H alkylation of *o*-aminoaryldiazomethanes.

of TEMPO could be directly detected by HRMS (Fig. S3†) and also spin-trapped by phenyl *N-tert*-butylnitrone (PBN) to exhibit the characteristic EPR signals (Fig. S4†).

To gather further evidence for the stepwise radical mechanism, we designed specific substrates as radical probes to shed light on the nature of ε-Co(III)-aminoalkyl radical intermediates. First, allylic C–H substrate **1u** was prepared as a radical resonance probe to evaluate potential olefin isomerization *via* the resulting allylic radical intermediate after 1,5-HAA (Scheme 2b). As observed for **1c** (Scheme 2a), a similar bis-TEMPO-capped compound **3u** was isolated in 72% yield without formation of the corresponding C–H alkylation product (Scheme 2b). Characterizations of **3u** revealed that the C=C double bond was isomerized from the terminal to internal position (Scheme 2b). Clearly, the resulting ε-Co(III)-aminoalkyl radical, which can be represented by its two resonance forms **1u-A** and **1u-B** as an allylic radical, was captured by TEMPO to give intermediate **1u-C** and then underwent further radical substitution with second TEMPO to deliver **3u**. The predominant production of **3u** is presumably a result of the much faster capping rate of **1u-B** (a primary radical) than **1u-A** (a secondary radical) by TEMPO radical. Second, substrate **1v** bearing a cyclopropyl ring was synthesized as a radical clock to examine ring-opening of the cyclopropylmethyl radical generated from 1,5-HAA (Scheme 2c). Interestingly, the reaction of **1v** by [Co(**P1**)] in the presence of TEMPO resulted in the formation of bis-TEMPO-capped compound **3v** in 40% yield as well as the C–H alkylation product **2v** in 30% yield. Obviously, the corresponding ε-Co(III)-aminoalkyl radical intermediate **1v-A** underwent two competitive pathways. While its radical substitution formed **2v**, the cyclopropylcarbinyl radical in **1v-A** also proceeded ring-opening competitively to generate homoallylic alkyl radical **1v-B**, which was transformed to the enamine **3v** upon two sequential captures by TEMPO *via* intermediate **1v-C**. The fact that **2v** and **3v** were produced in similar yields indicated that the forming rate of C2–C3 bond *via* radical substitution to construct the indoline ring was fast.[14]

Conclusions

In summary, the new Co(II)-based metalloradical system for enantioselective radical alkylation of C(sp^3)–H bonds has been developed for stereoselective synthesis of chiral indolines through asymmetric C2–C3 bond formation. Supported by the new ligand 2,6-DiPhO-QingPhyrin, this Co(II)-catalyzed system can activate *in situ* generated *ortho*-aminoaryldiazomethanes at room temperature for stereoselective radical alkylation of different types of C(sp^3)–H bonds with varied electronic and steric properties. In addition to chemoselectivity and regioselectivity, this radical system features functional group tolerance as well as compatibility with heteroaryl units. It represents a new synthetic application of Co(II)-based MRC and offers a streamlined construction of chiral 2-substituted indolines from readily available starting materials.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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