Heterocycles

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Intramolecular Radical Aziridination of Allylic Sulfamoyl Azides by Cobalt(II)-Based Metalloradical Catalysis: Effective Construction of Strained Heterobicyclic Structures

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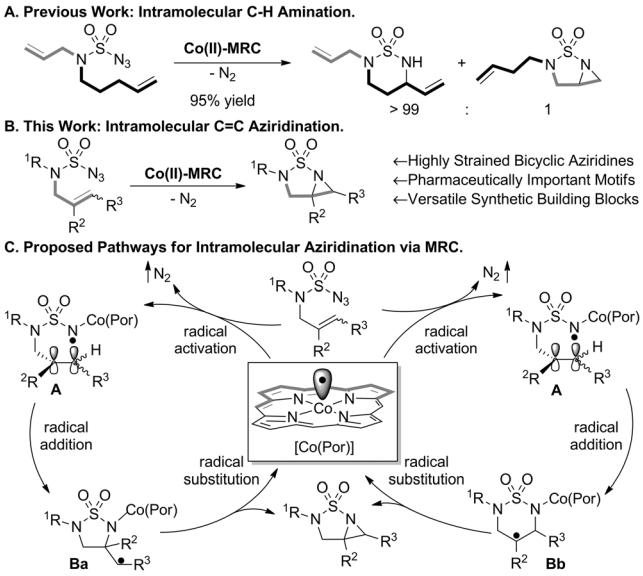
Abstract: *Cobalt(II)-based metalloradical catalysis (MRC) has been successfully applied for effective construction of the highly strained 2-sulfonyl-1,3-diazabicyclo[3.1.0]hexane structures in high yields through intramolecular radical aziridination of allylic sulfamoyl azides. The resulting [3.1.0] bicyclic aziridines prove to be versatile synthons for the preparation of a diverse range of 1,2- and 1,3-diamine derivatives by selective ring-opening reactions. As a demonstration of its application for target synthesis, the metalloradical intramolecular aziridination reaction has been incorporated as a key step for efficient synthesis of a potent neurokinin 1 (NK_1) antagonist in 60% overall yield.*

Radical chemistry has displayed vast potential in modern organic synthesis as it has many attractive features which are complementary to ionic chemistry.[1] To address the existing challenges in the field,[2] metalloradical catalysis (MRC) presents a new approach to achieving controllable reactivities and selectivities through catalytic generation of metal-stabilized organic radicals, such as the fundamentally new α-Co^{III}-alkyl and α-Co^{III}-aminyl radicals.[3,4] For example, the α-Co^{III}-aminyl radicals (also known as cobalt(III) nitrene radicals), which can be generated through a unique radical-transfer process from the cobalt-centered radicals of cobalt(II) porphyrins [Co(Por)] to organic azides upon metalloradical activation,[3e–g] have demonstrated controlled reactivities for both hydrogen atom abstraction of C–H bonds and radical addition to C=C bonds to furnish a catalytic radical amination[5] and aziridination,[6] respectively, with high levels of selectivity. In particular, the cobalt(II)-based MRC system exhibits remarkable chemoselectivity, as exemplified by the selective transformation of the sulfamoyl azide containing both *N*-allyl and *N*-bis(homoallyl) groups (Scheme 1 A). Exclusive intramolecular 1,6-radical amination of the allylic C–H bonds was reported and there was no observation of the potential intramolecular radical aziridination of the C=C bonds.[5e] In the absence of the more reactive *N*-bis(homoallyl) group, however, it was unclear if intramolecular aziridination of *N*-allyllic sulfamoyl azides was possible in view of the high strain associated with the resulting 2-sulfonyl-1,3-diazabicyclo[3.1.0]hexane structure (Scheme 1 B).[7] This type of catalytic process (Scheme 1 C) would require the corresponding α-Co^{III}-aminyl radical **A** to undergo efficient intramolecular addition to the olefin unit to generate either the γ-Co^{III}-alkyl radical intermediate **Ba** (Scheme 1 C; left: 5-*exo-trig* cyclization) or the γ-Co^{III}-alkyl radical **Bb** (Scheme 1 C; right: 6-*endo-trig* cyclization), followed by 3-*exo-tet* radical cyclization to deliver the aziridine product with regeneration of the [Co(Por)] catalyst. If successful, this catalytic transformation would be highly useful as the resulting [3.1.0] heterobicyclic structures are the key motifs in compounds of medicinal importance, and can also serve as versatile building blocks for the preparation of functionalized diamines.[8–11]



Scheme 1. Cobalt(II)-based metalloradical catalysis (MRC) for intramolecular C–H amination versus intramolecular C=C aziridination of allylic sulfamoyl azides

A number of catalytic systems have been successfully developed for intramolecular aziridination of olefins.[12–15] While several types of [*n*.1.0] heterobicyclic structures have been synthesized,[13–15] there is no previous report on the synthesis of [3.1.0] bicyclic sulfamoyl aziridines by catalytic intramolecular aziridination (Scheme 1 B).[7] This lack of

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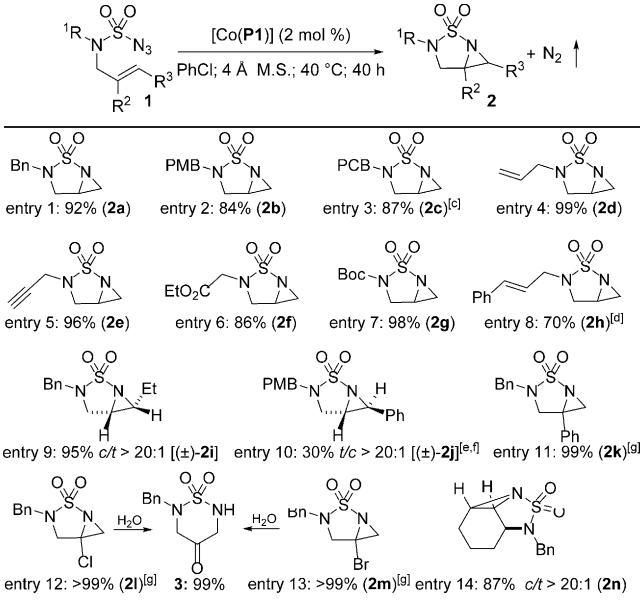
precedent is presumably due to the high ring strain of the bicyclic transition state associated with the concerted asynchronous mechanism of most intramolecular catalytic systems involving metallonitrenes as the key intermediates. We envisioned that the cobalt(II)-based MRC could potentially address this challenge by constructing the bicyclic structure through a stepwise ring formation in two separate radical cyclization steps (Scheme 1 C). Herein we report the development of the first catalytic system for intramolecular aziridination with allylic sulfamoyl azides by cobalt(II)-based MRC, thus allowing effective construction of the highly strained 2-sulfonyl-1,3-diazabicyclo[3.1.0]hexane structure in high yields. By taking advantage of the high strain, the resulting sulfonylated [3.1.0] bicyclic diaza aziridine products can be efficiently utilized as a new synthon for the preparation of 1,2- and 1,3-diamine derivatives by selective ring-opening reactions in an *exo*- and *endo*-fashion, respectively.

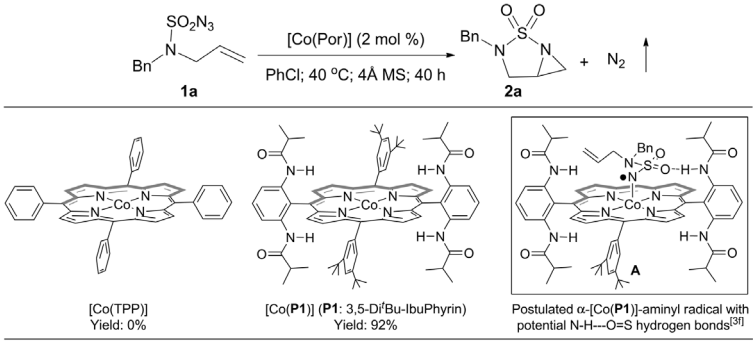
At the outset of this project, *N*-benzyl-*N*-allyl-sulfamoyl azide (**1a**), which was prepared from the corresponding amine in one step,[5d] was selected as a model substrate to explore the possibility of cobalt(II) MRC for intramolecular aziridination of allylic sulfamoyl azides and to establish effective catalytic conditions (Scheme 2). While the metalloradical catalyst [Co(TPP)] (TPP = tetraphenylporphyrin) was ineffective, [Co(**P1**)], in which the D_{2h}-symmetric porphyrin 3,5-di-^{t}Bu-IbuPhyrin **P1** has amide functionalities at the *ortho*-positions of the meso-phenyl groups,[6b] could effectively catalyze the intramolecular aziridination reaction under mild reaction conditions without the need for other reagents or additives, thus affording the desired sulfonylated [3.1.0] bicyclic diaza aziridine **2a** in 92% yield with N_2 as the sole byproduct. The dramatic difference in catalytic activity between [Co(TPP)] and [Co(**P1**)] is a remarkable demonstration of ligand-accelerated catalysis and could be rationalized as the outcome of hydrogen-bonding stabilization of a cobalt(III) aminyl radical intermediate.[3f]

Under the optimized reaction conditions (2 mol% of [Co(**P1**)] in PhCl at 40 °C for 40 h), the cobalt(II)-based intramolecular aziridination was found to have a broad substrate scope for a wide range of allylic sulfamoyl azides (Table 1). In addition to the *N*-benzyl group (Bn) in **1a** (entry 1), the metalloradical system could tolerate a variety of *N*-substituted functionalities because of its neutral and non-oxidative conditions, as demonstrated by the high-yielding aziridination reactions of the allylic sulfamoyl azides **1b–e** which contain 4-methoxybenzyl (PMB), 4-chlorobenzyl (PCB), allyl, and propargyl groups, respectively (entries 2–5). It is worth noting that these electron-rich *N*-substituents could be oxidatively degraded in other catalytic systems which require the use of a stoichiometric amount of oxidant, such as $PhI(OAc)_2$ or PhI=O.[15] Similarly, allylic sulfamoyl azides bearing electron-withdrawing groups were also suitable substrates for the catalytic system. For example, azides bearing *N*-ethoxycarbonyl (**1f**) and *N*-Boc (**1g**) groups underwent intramolecular aziridination to generate the corresponding bicyclic aziridines **2f** and **2g** in 86 and 98% yields, respectively (entries 6 and 7). Besides the tolerance of various functional groups, the cobalt(II)-catalyzed aziridination process shows interesting regioselectivity. For example, when the azide **1h**, containing both internal and terminal olefins, was utilized as the substrate, the aziridine **2h** was isolated in 70% yield as the sole product, thus indicating preferred reactivity of less sterically hindered terminal olefins over internal olefins (entry 8). In the absence of terminal olefins, however, both *cis* and *trans* internal olefins could also successfully undergo aziridination with stereospecificity (entries 9 and 10). Presumably also because of the steric effect, the *cis*-olefin-derived azide **1i** (entry 9) was found to be more reactive than the *trans*-olefin-derived azide **1j** (entry 10), thus resulting in stereospecific formation of the corresponding aziridines **2i** and **2j** in 95 and 30% yields, respectively. Interestingly, it

Table 1: Intramolecular aziridination of allylic sulfamoyl azides by [Co(**P1**)].[a,b]



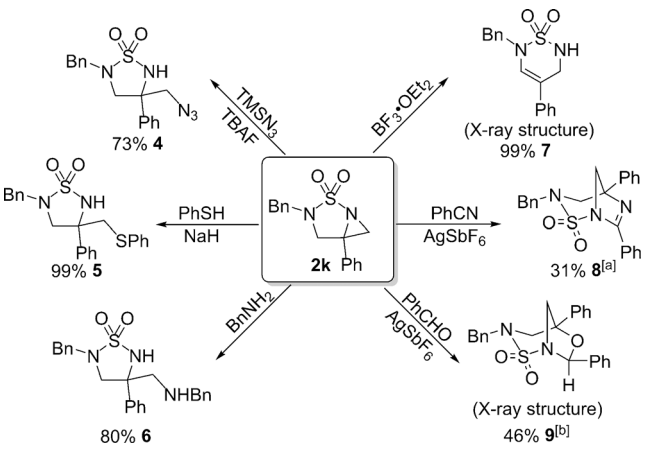
[a] Performed under N_2; [azide **1**]: 0.08 M. [b] Yield of isolated product. [c] PCB = *para*-chlorobenzyl. [d] with 30% azide recovered. [e] PMB = *para*-methoxybenzyl. [f] In PhCl at 80 °C; with 60% azide recovered. [g] 0.5 mol % [Co(**P1**)] for 8 h. Boc = *tert*-butoxycarbonyl.



Scheme 2. Ligand effect on [Co(Por)]-catalyzed intramolecular aziridination of allylic sulfamoyl azide: Importance of potential hydrogen-bonding interactions. M.S. = molecular sieves.

was found that allylic azides derived from disubstituted terminal olefins exhibited even higher reactivity. For example, at a catalyst loading as low as 0.5 mol% and in much shorter reaction time (8 h), the
2-phenyl allylic azide **1k** effectively underwent aziridination by [Co(**P1**)], thus affording the desired sulfonylated [3.1.0] bicyclic diaza aziridine **2k** in nearly quantitative yield (entry 11). It is worth noting the exceedingly high strain of the 2-sulfonyl-1,3-diazabicyclo[3.1.0]hexane structure in **2k** where the two bridgeheads are a quaternary carbon center and a tertiary nitrogen center, respectively. As an additional example, the intramolecular aziridination reaction of the 2-chloro-allylic azide **1l** could be facilely catalyzed by [Co(**P1**)] to afford the corresponding chloro-[3.1.0] bicyclic diaza aziridines **2l** in full conversion (entry 12). Although the tertiary alkyl chloride **2l** could be characterized by both ^{1}H and ^{13}C NMR spectroscopy (see the Supporting Information), it underwent a subsequent ring-opening reaction during the purification, thus affording the ketone product **3** in nearly quantitative yield (entry 12). The ready formation of **3** is presumably a result of the unusual kinetic susceptibility of the bridgehead quaternary amino halide units to halide substitution by water and subsequent rearrangement. Similarly, the 2-bromo-allylic azide **1m** could also be converted into **3** in an excellent yield, presumably via the initial aziridination product bromo-[3.1.0] bicyclic diaza aziridines **2m** (entry 13). Remarkably, even the cyclohexene-derived azide **1n** could be successfully employed as the substrate for the cobalt(II)-based intramolecular aziridination, thus allowing construction of the highly strained tricyclic aziridine **2n** in 87% yield with excellent control of diastereoselectivity (entry 14). It is noted that **2n** and related fused tricyclic aziridine compounds may serve as useful precursors for preparation of the valuable 1,2,3-cyclohexanetriamine motif which has been found in a number of biologically and pharmaceutically important compounds.[9]

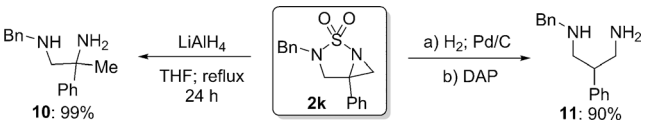
In view of the high ring strain associated with the 2-sulfonly-1.3-diazabicyclo[3.1.0]hexane structure, we then turned our attention to explore further transformations of **2**. In particular, we were interested in the possibility of regioselectively opening the bicyclic rings of these compounds. By using **2k** as a representative example, the three-membered aziridine ring of the bicyclo[3.1.0] structure was regioselectively opened at the *exo*-position by various nucleophiles (Scheme 3). For example, **2k** could be effectively opened by trimethylsilyl azide, thiophenol, and benzylamine under mild reaction conditions to afford the corresponding five-membered thiadiazolidine dioxide derivatives **4**–**6** in good to excellent yields. In addition to *exo*-ring opening reactions by nucleophiles, we also demonstrated the selective *endo*-ring opening at the bridgehead position of the bicyclo-[3.1.0] structure in the presence of Lewis acids.[10] When treated with $BF_3{\cdot}OEt_2$, **2k** was regioselectively opened to form the thiadiazine dioxide **7** in quantitative yield, presumably via a 1,3-dipole intermediate.[10] The structure of **7** was confirmed by X-ray crystallographic analysis (see the Supporting Information). In the presence of $AgSbF_6$, the resulting 1,3-dipole intermediate from **2k** could be partially trapped by dipolarophiles such as benzonitrile and benzaldehyde to form



Scheme 3. Regioselective ring-opening reactions of the [3.1.0] bicyclic aziridine **2k** by various reagents. [a] Isolated together with 59% of **7**. [b] Isolated together with 34% of **7**. TBAF = tetra-*n*-butylammonium fluoride, TMS = trimethylsilyl.

the tricyclic compounds **8** and **9**, respectively, in addition to the formation of **7**. X-ray crystallographic analysis (see the Supporting Inforrmation) established the unique [3.2.1] tricyclic structure of **9** as having four heteroatoms with tertiary nitrogen and quaternary carbon bridgeheads.

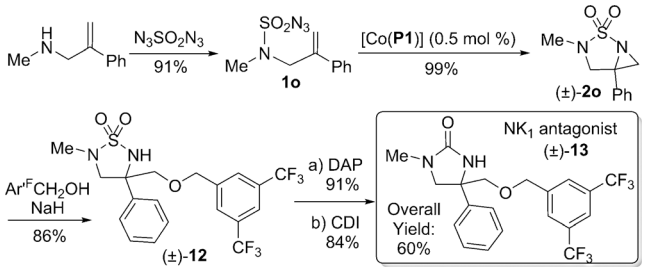
Considerable effort has been dedicated to the development of efficient methods for the preparation of diamines, which are prevalent motifs in biologically active molecules and can also function as chelating ligands for complexing transition metals.[11] Given that cyclic sulfamides can serve as precursors of diamines,[16] we show that the aziridines **2** can be efficiently desulfonylated for selective formation of either 1,2-diamines or 1,3-diamines, depending on the specific reaction conditions, as demonstrated with the reactions of **2k** (Scheme 4). When treated with $LiAlH_4$ in THF, **2k** was



Scheme 4. Selective reductive desulfonylation of bicyclic aziridine structure. THF = tetrahydrofuran.

selectively opened at the *exo*-position through facile removal of the sulfonyl group, thus producing the 1,2-diamine **10**, containing a quaternary chiral carbon center, in 99% yield. Alternatively, **2k** could be selectively converted into the 1,3-diamine **11** in 90% yield, by aziridine ring opening (*endo*) under H_2/Pd/C reduction conditions and subsequent desulfonylation by transamination with 1,3-diaminopropane (DAP).

To showcase the application of [Co(**P1**)]-catalyzed intramolecular aziridination of allylic sulfamoyl azides and the subsequent transformations of the resulting sulfonylated [3.1.0] bicyclic diaza aziridines for target synthesis, we developed a concise and high-yielding synthetic route to the bioactive compound **13** (Scheme 5),[17] one member of a family of potent Neurokinin 1 (NK_1) receptor antago-



Scheme 5. Application of the cobalt(II)-catalyzed intramolecular aziridination for the efficient synthesis of the potent NK_1 antagonist **13**. CDI = 1,1′-carbonyldiimidazole.

nists.[18] The compound **13** consists of a core structure of *N*-methylimidazolidin-2-one with a quaternary carbon center bearing phenyl and (3,5-bis(trifluoromethyl)benzyloxy)-methyl groups. Starting from *N*-methyl-2-phenylallylamine, the allylic sulfamoyl azide **1o** was readily prepared in 91% yield. The catalytic intramolecular aziridination of **1o** proceeded smoothly in the presence of only 0.5 mol % of [Co(**P1**)], thus affording the desired [3.1.0] bicyclic sulfamoyl aziridine **2o** in 99% yield on a gram scale. Upon treatment with bis(trifluoromethyl)benzyl alcohol (Ar'_FCH_2OH) in the presence of NaH, **2o** was regioselectively opened to give **12** in 86% yield. The cyclic sulfamide **12** was successfully transformed into the final cyclic urea analogue **13** through straightforward desulfonylation with DAP in 91% yield, and subsequent carbonylation with 1,1′-carbonyldiimidazole (CDI) in 84% yield. The five-step synthesis of **13** was achieved in an overall yield of 60%.[19]

In summary, we have developed the first synthetic tool for efficient construction of highly strained 2-sulfonaly-1,3-diazabicyclo[3.1.0]hexane structures through intramolecular radical aziridination by cobalt(II)-based MRC. The [Co(**P1**)]-catalyzed aziridination system, which operates under neutral and nonoxidative conditions, is generally applicable to a wide range of allylic sulfamoyl azides, thus allowing high-yielding synthesis of the bicyclic aziridine molecules with various substitution patterns. By taking advantage of the high strain associated with the unique heterobicyclic structure, we have demonstrated a series of synthetic applications of the resulting [3.1.0] bicyclic diaza aziridines as intermediates for preparation of valuable 1,2- and 1,3-diamines, and related derivatives. The catalytic method was also showcased as a key step in the high-yielding synthesis of the NK_1 antagonist **13**. Efforts are underway to study the detailed catalytic mechanism of this cobalt(II)-based radical intramolecular aziridination, as well as to develop an asymmetric variant.

Acknowledgements

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Keywords: aziridination · cobalt · heterocycles · metalloradical catalysis · radicals

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Communications

Heterocycles

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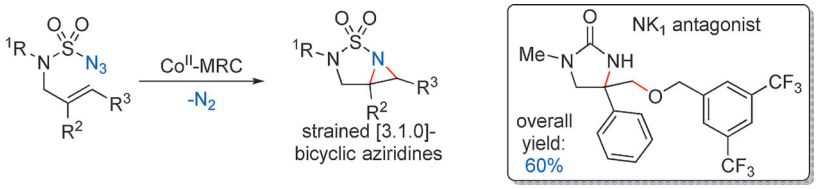
Intramolecular Radical Aziridination of Allylic Sulfamoyl Azides by Cobalt(II)-Based Metalloradical Catalysis: Effective Construction of Strained Heterobicyclic Structures



Co is key: Cobalt(II)-based metalloradical catalysis (MRC) delivers highly strained 2-sulfonyl-1,3-diazabicyclo[3.1.0]hexanes by intramolecular radical aziridination of allylic sulfamoyl azides. The aziridines are versatile synthons for the preparation of 1,2- and 1,3-diamines. The metalloradical aziridination reaction was used as a key step for the efficient synthesis of a neurokinin 1 (NK$_1$) antagonist.

