

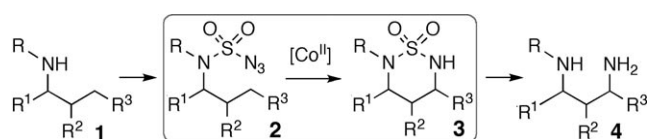
Selective Intramolecular C–H Amination through the Metalloradical Activation of Azides: Synthesis of 1,3-Diamines under Neutral and Nonoxidative Conditions**

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Amino groups exist ubiquitously in natural products and synthetic molecules, and play key roles in a wide range of important applications. Consequently, immense effort has been devoted to the development of efficient and selective processes for the preparation of amines.^[1] Among different approaches, the catalytic amination of abundant C–H bonds on the basis of a metal-mediated nitrene-insertion pathway is one of the most general and direct methods for installing nitrogen functionalities.^[2] The promise of this approach as a synthetically useful methodology has been demonstrated with a number of intramolecular C–H amination processes through the combined use of Rh^{II}-based catalysts and iminoiodane nitrene sources.^[2,3] Notably, Du Bois and co-workers elegantly demonstrated that N-Boc-protected sulfamides could be selectively converted into cyclic sulfamides by [Rh₂(esp)₂] in combination with PhI(OAc)₂ and MgO to provide access to synthetically useful 1,3-diamines (esp = $\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionate).^[4] The Rh^{II}-based intramolecular amination was shown to be effective for both secondary and tertiary C–H bonds with stereospecificity and high diastereoselectivity. However, the amination of strong primary C–H bonds had yet to be demonstrated.^[5] Moreover, the catalytic system was unsuitable for simple N-alkyl sulfamides, which were oxidatively degraded by the stoichiometric oxidant, PhI(OAc)₂.^[4]

As stable metalloradicals, cobalt(II) complexes of porphyrins, [Co(Por)], have emerged as a new class of catalysts for C–H amination.^[6] The cobalt(II)-based metalloradical amination (MRAM) is different from the commonly studied Rh₂ system, as it can operate effectively with various azide substrates without the need for terminal oxidants and other additives.^[7–11] To further validate the utility of C–H amination methodology based on a cobalt(II) catalyst and azides, we envisioned a general strategy for the synthesis of 1,3-diamines from monoamines through the key step of the intramolecular C–H amination of sulfamoyl azides with [Co(Por)] (Scheme 1). We report herein a cobalt(II)-based catalytic

system that is highly effective for the intramolecular 1,6-C–H amination of sulfamoyl azides to furnish six-membered cyclic sulfamides. Not only excellent regioselectivity, but also high diastereoselectivity and stereospecificity were observed with the catalytic system. The cobalt(II)-catalyzed amination is operationally simple, as it proceeds under neutral and non-oxidative conditions without the need for other reagents, and N₂ is the only byproduct. Consequently, the degree of functional-group tolerance is high, and the reaction can be applied to substrates with various substituents, such as oxidizable amide and sulfide groups. An important feature of this catalytic system is the effective amination of strong primary C–H bonds, as well as secondary and tertiary C–H bonds.



Scheme 1. Cobalt(II)-catalyzed intramolecular C–H amination of sulfamoyl azides under neutral and nonoxidative conditions: general synthetic strategy for 1,3-diamine derivatives.

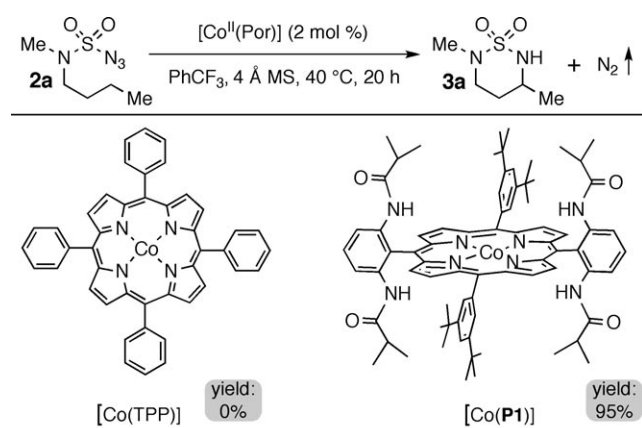
A wide range of sulfamoyl azides **2** were conveniently prepared from the corresponding amines **1** on the basis of reported procedures (see the Supporting Information).^[12,13] At the outset of this project, we selected the simple azide **2a** as a model substrate to explore the possibility of the cobalt(II)-catalyzed intramolecular C–H amination of sulfamoyl azides and to establish effective reaction conditions (Scheme 2). Although nonfunctionalized [Co(TPP)] was found to be an ineffective catalyst, [Co(**P1**)], in which the *D*_{2h}-symmetric porphyrin 3,5-Di*t*Bu-IbuPhyrin, **P1**, has amide functionalities at the *ortho* positions of two *meso* phenyl groups, effectively catalyzed the intramolecular amination of **2a** through a selective 1,6-C–H nitrene-insertion process under mild conditions (Scheme 2). Owing to the absence of oxidants or other additives, the cobalt(II)-catalyzed reaction proceeded cleanly to afford the desired six-membered cyclic sulfamide **3a** as essentially the only product in 95 % yield (the by-product was nitrogen gas). The difference in catalytic reactivity between [Co(TPP)] and [Co(**P1**)] can be considered as a dramatic demonstration of ligand-accelerated catalysis and could be rationalized as the outcome of a potential

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[**] We are grateful for financial support by the National Science Foundation (CAREER Award: CHE-0711024).

Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/anie.201005552>.

hydrogen-bonding interaction between the S=O and N–H groups in the supposed nitrene intermediate.^[6b,14]



Scheme 2. Effect of the porphyrin ligand on the cobalt(II)-catalyzed C–H amination of sulfamoyl azides: importance of potential H bonding. MS=molecular sieves.

Under optimized conditions (with [Co(**P1**)] (2 mol %) in PhCF₃ at 40 °C for 20 h), the cobalt(II)-catalyzed C–H amination system was found to be applicable to a wide range of sulfamoyl azides (Table 1). Besides the N-methyl group in **2a**, the catalytic system tolerated a variety of N substituents because of the neutral and nonoxidative conditions: azides **2b**, **2c**, and **2d**, which contain ester, primary-amide, and sulfide functional groups, respectively, underwent high-yielding amination reactions (Table 1, entries 1–4). Predictably, benzylic C–H bonds could also be effectively aminated to provide the desired six-membered cyclic sulfamides in high yields (Table 1, entries 5 and 6). The regioselectivity for 1,6-C–H nitrene insertion was best demonstrated with azide **2g**, in which only one of the five CH₂ units was selectively aminated to provide the corresponding cyclic sulfamide **3g** in 90 % yield (Table 1, entry 7).

The cobalt(II)-catalyzed 1,6-C–H nitrene-insertion process proceeded equally well with tertiary C–H bonds, as illustrated by the amination of sulfamoyl azides **2h** and **2i** (Table 1, entries 8 and 9). Remarkably, even unactivated strong primary C–H bonds could be successfully aminated with this catalytic system, as exemplified by the high-yielding reactions of substrates **2j** and **2k** (Table 1, entries 10 and 11). Furthermore, the cobalt(II)-based catalytic system could be effectively utilized for the intramolecular amination of heteroatom-activated C–H bonds, such as the C–H bonds adjacent to an amide substituent in **2l** and an ether group in **2m**; the valuable N,N-acetal **3l** and N,O-acetal **3m** were obtained in high yields (Table 1, entries 12 and 13).

By taking advantage of the instability of N,O-acetals towards the formation of iminium ions, the amination product **3m** could be transformed directly into other cyclic sulfamides.^[15] Thus, the N,O-acetal **3m** formed by the amination of azide **2m** was converted in situ into the unsubstituted cyclic sulfamide **4m** by reduction with NaBH₄ and into the homoallyl-substituted cyclic sulfamide **5m** by treatment

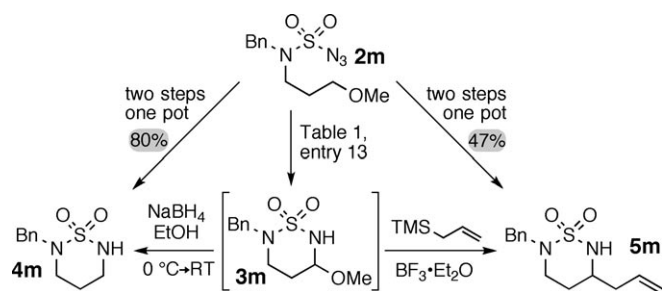
Table 1: Catalytic intramolecular amination of different classes of C–H bonds through the activation of sulfamoyl azides by [Co(**P1**)].^[a]

Entry	Sulfamoyl azide	Cyclic sulfamide	Yield [%] ^[b]
1	2a R = Me	3a	95
2	2b R = CH ₂ CO ₂ Et	3b	99
3 ^[c]	2c R = CH ₂ CONH ₂	3c	99
4 ^[d]	2d R = CH ₂ (<i>p</i> -MeS)C ₆ H ₄	3d	92
5	2e R = Et	3e	94
6	2f R = CH ₂ CF ₃	3f	95
7 ^[e]	2g	3g	90
8	2h R ¹ = CH ₂ CH ₂ <i>i</i> Pr; R ² = Me	3h	92
9 ^[e]	2i R ¹ = Bn; R ² = Et	3i	95
10 ^[e]	2j R = Me	3j	96
11 ^[e]	2k R = Ph	3k	87
12 ^[e]	2l	3l	91
13	2m	3m	> 80 ^[f]

[a] Reaction conditions: [Co(**P1**)] (2 mol %), PhCF₃ (solvent), 4 Å MS, 40 °C, 20 h, N₂ atmosphere; [**2**] = 0.10 M. [b] Yield of the isolated product. [c] The reaction was carried out in benzene. [d] The reaction was carried out in benzene at 80 °C for 3 h. [e] The reaction was carried out in benzene with [Co(**P1**)] (4 mol %). [f] Estimated yield based on the further transformation of **3m** (see Scheme 3), which could not be isolated owing to instability. Bn = benzyl, TBS = *tert*-butyldimethylsilyl.

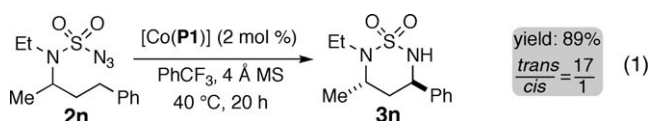
with an allyl silane in the presence of BF₃·OEt₂ (Scheme 3). The ability to carry out these two-step transformations in a one-pot procedure without any preworkup of the amination reaction mixture owing to the absence of oxidants and other additives in the catalytic system further enhanced the practicality of these synthetic operations.

To assess the diastereoselectivity of the [Co(**P1**)]/azide-based catalytic process, we carried out the C–H amination reaction of substrate **2n** under standard conditions. The



Scheme 3. One-pot, two-step transformations of sulfamoyl azide **2m** via the heterocyclic N,O-acetal intermediate **3m**. TMS = trimethylsilyl.

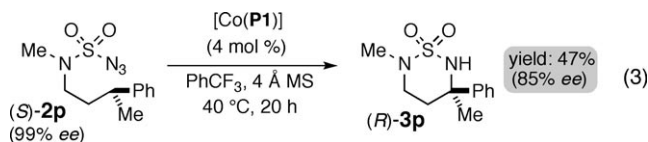
desired cyclic sulfamide **3n** was obtained in 89% yield with a high diastereomeric ratio of 17:1 in favor of the *trans* isomer [Eq. (1)]. The relative configuration of *trans*-**3n** was further



confirmed by X-ray crystallographic analysis (see the Supporting Information). When the optically pure sulfamoyl azide (*R*)-**2o** was used as the substrate under similar conditions, the reaction catalyzed by [Co(**P1**)] resulted in the high-yielding formation of the corresponding C–H amination product (*R,R*)-**3o** with excellent diastereoselectivity [Eq. (2)].

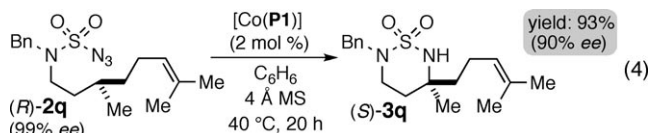


We performed further experiments to evaluate the potential stereospecificity of the cobalt(II)-catalyzed C–H amination. Thus, the enantiomerically pure sulfamoyl azide (*S*)-**2p** containing a tertiary C–H bond was prepared and subjected to catalysis by [Co(**P1**)] [Eq. (3)]. Presumably as a

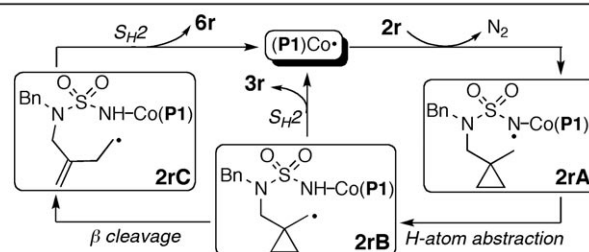
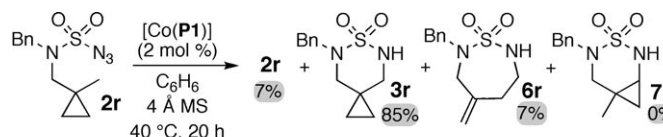


result of the greater steric hindrance around the tertiary C–H bond and potential stabilization of the tertiary carbon radical intermediate by the phenyl group (see below), the resulting amination product **3p** was obtained in lower yield than the products derived from the aforementioned substrates **2h** and **2i** with tertiary C–H bonds (Table 1, entries 8 and 9). HPLC

analysis on a chiral phase showed that the cyclic sulfamide (*R*)-**3p** had a decreased *ee* value of 85%, which indicates partial racemization during catalysis [Eq. (3)]. When the optically pure azide (*R*)-**2q**, in which the phenyl group at the tertiary carbon center of azide **2p** had been replaced with an alkyl group, was employed instead as the substrate (more similar to substrates **2h** and **2i**; Table 1, entries 8 and 9), both a high yield and high enantioselectivity were observed for the desired product (*S*)-**3q** of amination of the tertiary C–H bond [Eq. (4)]. The absolute configuration of (*S*)-**3q** was further confirmed by X-ray crystallographic analysis (see the Supporting Information).



Taken together with the radical nature of the Co^{II} catalyst, the reactivity and selectivity profiles observed in the reactions described above suggest that the [Co(**P1**)]-catalyzed intramolecular C–H amination of sulfamoyl azides might operate by a mechanism that is different from that of the commonly studied Rh₂-based amination system and which may involve a “radical nitrene” intermediate.^[6c] To shed more light on the suggested radical mechanism, we designed and synthesized sulfamoyl azide **2r**, which contains a cyclopropyl unit, as a radical probe substrate for [Co(**P1**)]-catalyzed amination. The major product (85% yield) of the C–H amination reaction of **2r** was the six-membered cyclic sulfamide **3r**, which resulted from 1,6-C–H nitrene insertion into the primary C–H bonds (ca. 100 kcal mol^{−1}; Scheme 4).^[16] Nota-

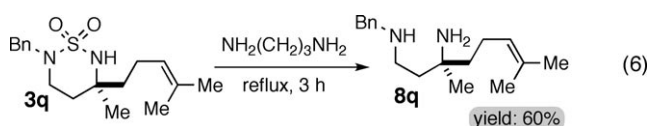
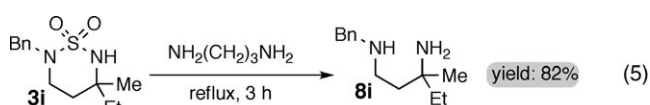


Scheme 4. Mechanism proposed on the basis of cyclopropyl-ring opening for the cobalt(II)-catalyzed intramolecular C–H amination.

bly, the potential product **7r** of amination of the more electron-rich but stronger secondary C–H bonds (ca. 106 kcal mol^{−1})^[16] was not observed. This result indicates that a key metallonitrene intermediate performs radical hydrogen-atom abstraction rather than electrophilic C–H activation. More

importantly, a small amount of the seven-membered cyclic sulfamide **6r**, a product of cyclopropyl-ring opening, was also generated (in 7 % yield) in the catalytic reaction. We propose that products **3r** and **6r** are derived from the same carbon-radical species **2rB**, which was generated from the key “radical nitrene” intermediate **2rA** by hydrogen-atom abstraction (Scheme 4).

The series of cyclic sulfamides **3** synthesized by the cobalt(II)-catalyzed C–H amination contain multiple functionalities and are potentially suitable for a variety of applications, for example, as enzyme inhibitors in medicinal chemistry.^[17] They can also serve as convenient precursors for the preparation of valuable 1,3-diamine derivatives (Scheme 1). Among various methods, the SO₂ unit can be effectively removed under neutral conditions in 1,3-diaminopropane at reflux by transamination,^[18] as exemplified by the conversion of sulfamides **3i** and **3q** into the corresponding 1,3-diamines **8i** and **8q** [Eqs. (5) and (6)].



In summary, a cobalt(II)-based catalytic system has been developed for the selective intramolecular C–H amination of a wide range of sulfamoyl azides under neutral and non-oxidative conditions. Together with the straightforward preparation of the azide substrates and the effective procedure for deprotection of the sulfone group, the high-yielding formation of cyclic sulfamides through the cobalt(II)-catalyzed amination process offers general access to valuable 1,3-diamine derivatives from the corresponding monoamines. The catalytic system has several salient features that overcome challenging problems for contemporary Rh₂-catalyzed amination, such as the amination of strong primary C–H bonds and functional-group tolerance. Fundamentally, the implied radical mechanism may have far-reaching impact on our understanding and the further development of catalytic C–H amination and related nitrene-transfer processes.

Received: September 5, 2010

Published online: November 25, 2010

Keywords: C–H amination · cobalt porphyrins · 1,3-diamines · nitrene transfer · sulfamoyl azides

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