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Cobalt(II)-Catalyzed Synthesis of Sulfonyl Guanidines *via* Nitrene Radical Coupling with Isonitriles: A Combined Experimental and Computational Study

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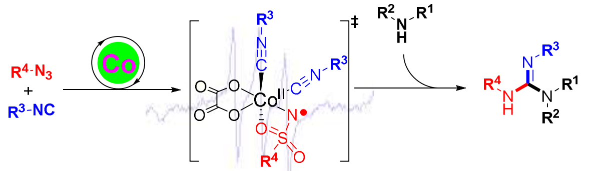
Supporting Information Placeholder

ABSTRACT: A Co(II)-catalyzed synthesis of sulfonyl guanidines by using amines, isonitriles, and organic azides as nitrene source has been developed. This protocol provides an environmentally-friendly, and simple strategy for the synthesis of sulfonyl guanidine derivatives by employing a range of substrates and will find potential applications in organic synthesis. The computational and EPR studies suggested the formation of guanidine derivatives *via* a cobalt-nitrene radical intermediate.



KEYWORDS: cobalt(II)-catalyzed, sulfonyl guanidines, amines, isonitriles, organic azides, nitrene, computational study

■ INTRODUCTION

Substituted guanidine moiety are widely found in biologically active molecules and natural products, such as Arginine,[1] Creatine,[2] Guanine,[3] Saxitoxin (STX),[4] (−)-Palau'amine,[5] Sulfaguanidine,[6] Pinacidil[7] (Figure 1). In view of their importance and usefulness, synthesis of guanidines has attracted great interest of organic and medicinal chemists. The reported strategies for synthesizing the guanidine derivatives can be generally classified into the following two types, one is solution synthesis[8] and another one is solid phase synthesis.[9] However, the traditional synthetic methodologies suffer from harsh reaction conditions, multistep synthesis, limited substrate scope, and/or expensive catalysts. Hence, the development of a broader pallet and efficient approach to substituted guanidines is highly desired.

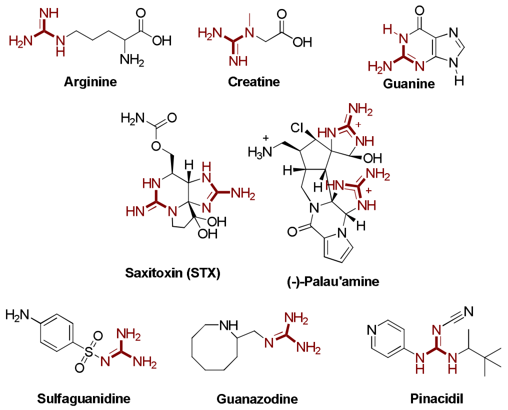
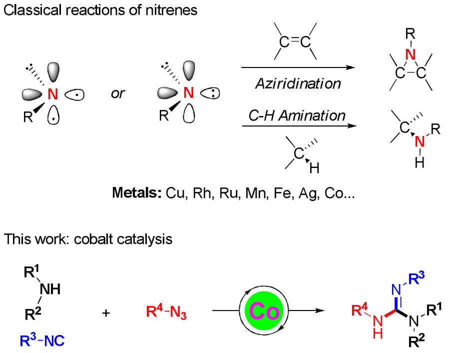


Figure 1. Guanidine-based bioactive molecules

Nitrene intermediates are among the most promising agents for selective introduction of nitrogen in molecules. Since the discovery of practical conditions for the generation of metallanitrenes, the chemistry of transition metal-nitrene radical intermediates has attracted significant attention due to the high reactivity in various nitrogen transfer reactions such as addition reactions, radical coupling reactions, as well as C-H activation reactions.[10] Furthermore, transition metal-coordinated nitrogen-centered radicals are generally more stable than free nitrogen-centered radicals, thus opening the door to potential catalytic applications.[11] In recent years, Zhang's group made great contribution to Co(II)-based metalloradical reactions such as radical C-H alkylation,[12] radical C-H amination,[13] radical olefin cyclopropanation[14] and radical aziridination.[15] In addition, computational studies of the Co(III)–nitrene radical species and their application in organic synthesis suggested that formation of the metallanitrenes was the key step in these reactions.[16] To the best of our knowledge, employing cobalt(III)-nitrene radical approach to produce guanidines has not been studied. Our group is interested in developing cobalt-catalyzed isocyanide insertion reactions to construct *N*-containing molecules. Herein, we describe the synthesis of sulfonyl guanidines by the reaction of cobalt-catalyzed reaction of azides, isonitriles and various amines involving cobalt(III)-nitrene radical intermediate (Scheme 1). The computational and EPR studies provide mechanistic insight into the formation of guanidine derivatives.

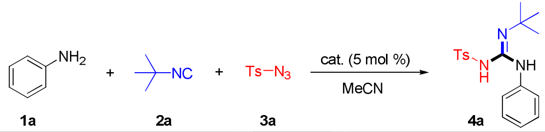
Scheme 1. Transition metal-catalyzed nitrile reactions



■ RESULTS AND DISCUSSION

Initially, we tried the reaction of aniline (**1a**) and isonitrile (**2a**) with benzenesulfonyl azide (**3a**) in MeCN at 80 °C for 12 h. The desired product (E)-N-(N'-tert-butyl-N-phenylcarbamimidoyl)-4-methylbenzenesulfonamide (**4a**) could be obtained in 25% LC-yield (Table 1, entry 1). Some transition metal catalysts such as $Co(OAc)_2$, $Cu(OAc)_2$, $Pd(OAc)_2$, and $FeCl_2$ were screened as well and we found that the cobalt salt showed the best catalytic activity (Table 1, entries 2-5). Then, more cobalt salts were tested for this reaction and it was found that the reaction was almost completed when CoC_2O_4 (cobalt oxalate) was used (Table 1, entries 6-8). Further optimization study indicated that temperature and the reaction time had great impact on this reaction (Table 1, entries 9-15). The three-component reaction showed very low reactivity at 50 °C (Table 1, entry 7), and with the reduction of the time, the yield of **4a** was obviously decreased.

Table 1. Screening of Reaction Conditions[a]



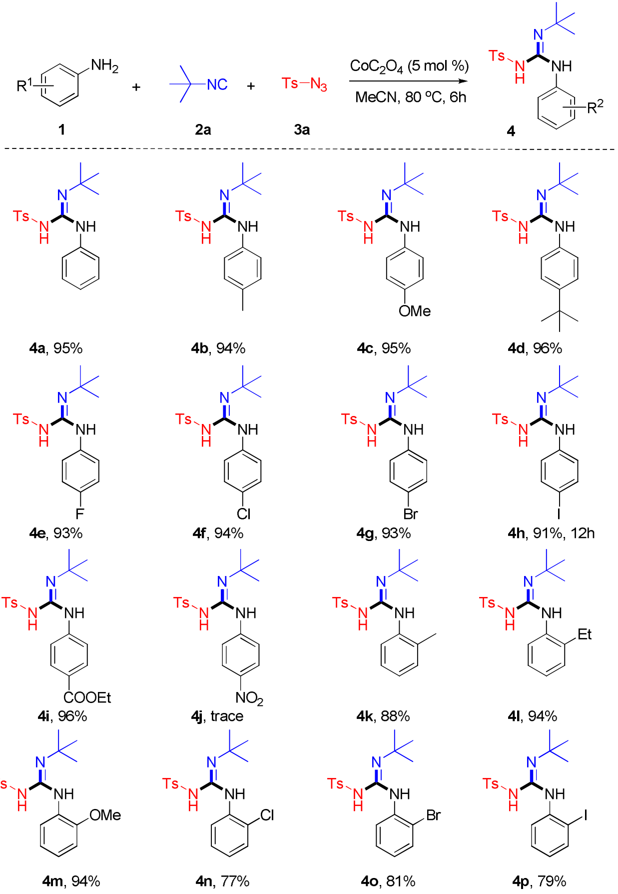
entry	cat. (5 mol %)	T (℃)	time (h)	yield (%)[b]
1	---	80	12	25
2	$Co(OAc)_2$	80	12	91
3	$Cu(OAc)_2$	80	12	13
4	$Pd(OAc)_2$	80	12	46
5	$FeCl_2$	80	12	17
6	$Co(acac)_2$	80	12	85
7	CoC_2O_4	80	12	99
8	$CoCl_2·6H_2O$	80	12	86
9	CoC_2O_4	60	12	80
10	CoC_2O_4	50	12	70
11	**CoC_2O_4**	**80**	**6**	**99(95)**[c]
12	CoC_2O_4	80	4	90
13	CoC_2O_4	80	2	81
14	CoC_2O_4	80	1	56

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), **3a** (0.75 mmol), catalyst (5 mol%), MeCN (3 mL) under air atmosphere. [b] The yields were determined by LC analysis using diphenyl as an internal standard. [c] Isolated yield.

With the optimized reaction conditions in hand, we first investigated the scope of various arylamines **1** (Scheme 2). It was gratifying to observe that para-substituted anilines with all kinds of electron-donating groups (Me, OMe, ^{t}Bu), halogen atoms (F, Cl, Br, I), and even COOEt group, exhibited a very high reactivity under optimized reaction condition (**4a-i**, 91-96%). However, only trace amount of product **4j** could be detected when 4-nitroaniline was used in this reaction. Then, some ortho-substituted anilines were also tested and we found electron-donating groups (Me, Et, OMe) could give the desired product **4k-m** in excellent yields (88-94%). The ortho-substituted anilines with halogen atoms (Cl, Br, I) displayed a lower reactivity than electron-donating groups and the desired product (**4n-p**) could be isolated in moderate to good yields (77-81%).

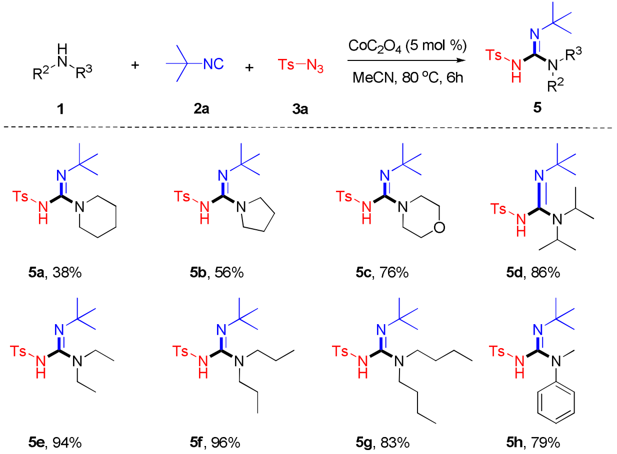
The substrate scope of the secondary amines was then examined (Scheme 3). We found that piperidine and pyrrolidine showed poor reactivity, leading to the desired products **5a** and **5b** in 38% and 56% yields, respectively. Furthermore, other secondary amines such as morpholine, diisopropylamine, diethylamine, dipropylamine, dibutylamine were applied in this reaction and showed better reactivity than piperidine and pyrrolidine, which gave 76-96% yields of products **5c-g**. Besides, the expected product **5h** could be isolated in 79% yield when *N*-methylaniline was used.

Scheme 2. Substrate scope of arylamines 1[a,b]



[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), **3a** (0.75 mmol), CoC_2O_4 (5 mol%), MeCN (3 mL) at 80 °C, 6 h under air atmosphere. [b] Isolated yield.

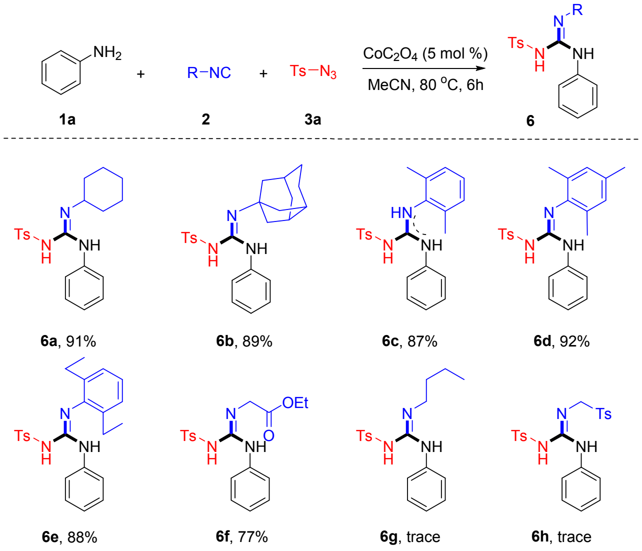
Scheme 3. Substrate scope of secondary amines 1[a,b]



[a] Reaction conditions: **1** (0.5 mmol), **2a** (0.6 mmol), **3a** (0.75 mmol), CoC_2O_4 (5 mol%), MeCN (3 mL) at 80 °C, 6 h under air atmosphere. [b] Isolated yield.

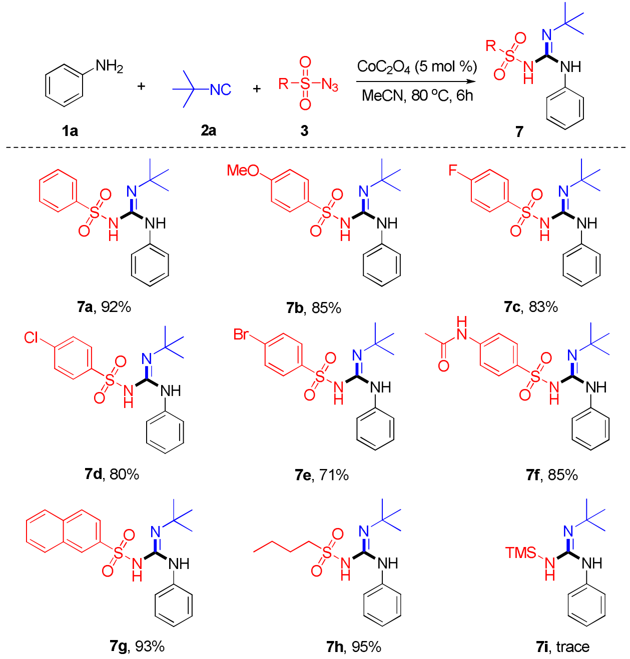
We next investigated the scope of isocyanides under the optimal conditions (Scheme 4). It was found that isocyanocyclohexane, 1-adamantyl isocyanide and different aryl isocyanides worked equally well to furnish the desired product **6a-e** in >87% yields. Notably, when isocyanide was substituted by functional groups such as ethyl isocyanoacetate, the corresponding product **6f** could also be obtained in 77% yield. Unfortunately, some other isocyanides such as 1-isocyanobutane and p-toluenesulfonylmethyl isocyanide decomposed under the established conditions and only trace amount of product could be detected.

Scheme 4. Substrate scope of isonitriles 2[a,b]



[a]Reaction conditions: **1a** (0.5 mmol), **2** (0.6 mmol), **3a** (0.75 mmol), CoC_2O_4 (5 mol%), MeCN (3 mL) at 80 °C, 6 h under air atmosphere. [b]Isolated yield.

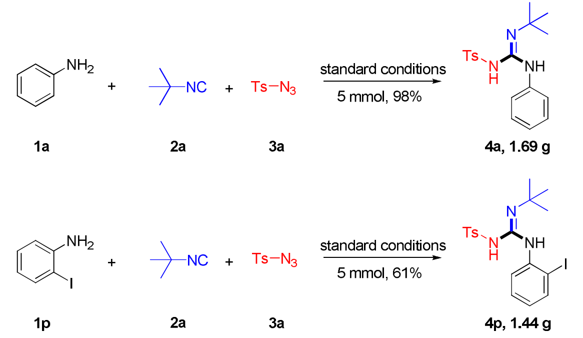
Scheme 5. Substrate scope of sulfonyl azides 3[a,b]



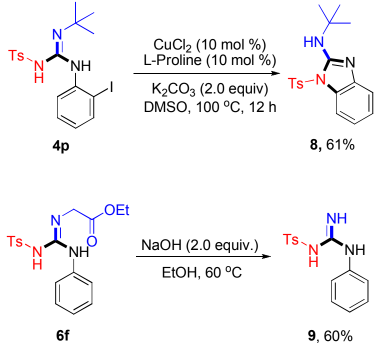
[a]Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), **3** (0.75 mmol), CoC_2O_4 (5 mol%), MeCN (3 mL) at 80 °C, 6 h under air atmosphere. [b]Isolated yield.

Then, we investigated the scope of organic azides **3** (Scheme 5). A variety of sulfonyl azides bearing different functional groups were tested. Various kinds of substituents, such as H, OMe, F, Cl, and even Br, were well tolerated. The 4-acetamidobenzenesulfonyl azide and naphthalene-2-sulfonyl azide gave the products **7f** and **7g** in 85% and 93% yields, respectively. Besides arylsulfonyl azides, alkylsulfonyl azide **3h** also exhibited a good reactivity in this transformation, producing the target product **7h** in 95% yield. However, only trace amount of product **7i** could be detected when azidotrimethylsilane was used in this reaction.

Scheme 6. Gram-scale synthesis of products 4a and 4p.



Scheme 7. Synthetic transformation of product 4p and 6f.



For the reaction to be synthetically useful, we tried two gram-scale reactions under standard conditions and the products **4a** and **4p** could be obtained in 98% and 61% yields, respectively (Scheme 6). To explore the potential application of the prepared derivatives **4p** and **6f** (Scheme 7). We first tried the reaction of **4p** in DMSO solvent at 100 °C for 12 h, catalyzed by 10 mol % $CuCl_2$ and 10 mol % L-proline in the presence of 2 equiv of K_2CO_3 and the desired product *N*-tert-butyl-1-tosyl-1H-benzo[d]imidazol-2-amine **8** was isolated in 61% yield. Furthermore, the transformation of **6f** could easily undergo reaction with 2 equiv of NaOH in ethanol, providing the corresponding 4-methyl-N-(N-phenylcarbamimidoyl)benzenesulfonamide **9** in 60% yield.

Computational studies were carried out to obtain an in-depth understanding for the mechanism of Co(II)-catalyzed synthesis of sulfonyl guanidines (see SI for computational details). According to the experimental results, the desired product could be formed in 25% yield even in the absence of the Co(II) catalyst. Thus, the possible pathways leading to the product in the absence and in the presence of the Co(II) catalyst were computationally considered, respectively. In the absence of the Co(II) catalyst, the initial step of dissociation of N_2 from sulfonyl azide (**3a**) to afford the triplet nitrene intermediate ^{3}**INT2** was calculated to have a free energy barrier of 35.6 kcal/mol (Figure 2).[17] Subsequently, the formed ^{3}**INT2** could attack isocyanide (**2a'**)[18] to yield triplet-state intermediate ^{3}**INT3**, which requires an activation energy of 14.2 kcal/mol. Afterwards, the triplet-state intermediate ^{3}**INT3** could convert to singlet ground state to form **INT4** intermediate via intersystem crossing (ISC). Alternatively, one may suggest that the attack of the terminal carbon of isocyanide to the N^{1} of sulfonyl azide to release N_2 could also afford **INT4** in a concerted fashion. Computational results show that the concerted pathway has a much higher energy barrier (45.2 kcal/mol) (see SI, Figure S1), indicating the formation of **INT4** in a stepwise manner might be more feasible. Next, another substrate, $PhNH_2$ (**1a**), could undergo nucleophilic attack to the central carbon of **INT4**, leading to intermediate **INT6** (Figure 2). The predicted $\Delta G^{\ddagger}$ is 28.9 kcal/mol for this step relative to **INT4**. From **INT6**, the subsequent proton transfer step could be followed to furnish the desired product. Computational studies suggest that the intermolecular stepwise proton transfer manner with the assistance of another $PhNH_2$ molecule would be a favorable pathway. The additional $PhNH_2$ could form H-bonds with the added $PhNH_2$ moiety (N^4-H…N^3) and the sulfonyl group (N^4-H…O) in **INT7**. The proton transfer from N^3 to N^4 was predicted to have a lower energy barrier (Figure 3). Next, the formed $PhNH_3^+$ species could donate the additional proton to N^1 to yield the desired product. The second proton transfer is also a facile step. Thus, the stepwise intermolecular proton transfer process was found to be a favorable pathway from **INT6** to the desired product.[19] The rate-limiting step for the formation of the desired product in the absence of the Co(II) catalyst would be the dissociation of N_2 from the sulfonyl azide.

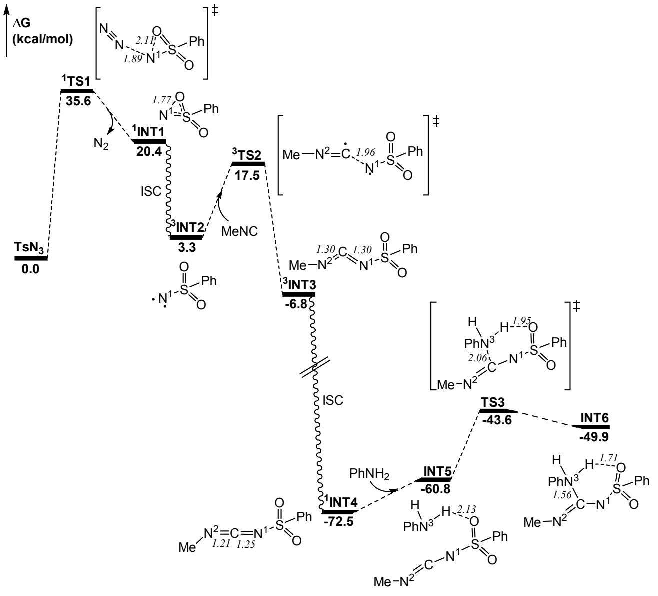


Figure 2. Energy profile (in kcal/mol) for the dissociation of N_2 from sulfonyl azide to yield the nitrene intermediate and subsequent reaction with isocyanide. Bond lengths are shown in Å.

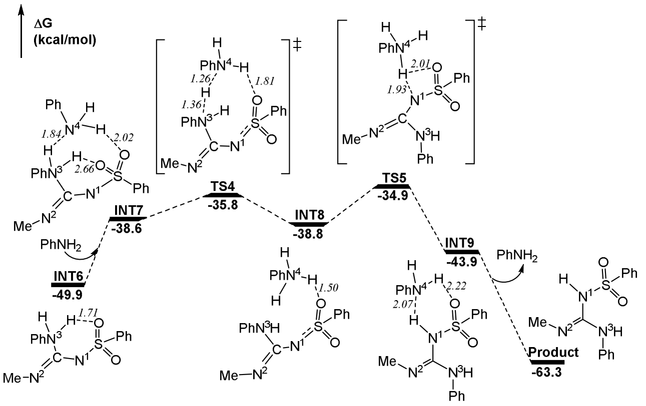


Figure 3. Energy profile (in kcal/mol) for the conversion of **INT6** to the desired product via proton transfer steps. Bond lengths are shown in Å.

To consider the catalytic role of Co(II) catalyst, the four-coordinated CoC_2O_4 with two MeCN solvent molecules as ligands was employed as an initial model. Subsequently, two isocyanide molecules and one sulfonyl azide molecule may undergo ligand exchange to afford a six-coordinated complex **INT12**. The dissociation of N_2 from the sulfonyl azide in **INT12** was calculated to have an energy barrier of 19.9 kcal/mol, relative to **INT12** (Figure 4). Thus, the presence of the Co(II) catalyst could efficiently lower the energy barrier of the dissociation of N_2 from the sulfonyl azide to generate the nitrene moiety.[20] Subsequently, the formed Co(III)-nitrene intermediate (**INT13**) might undergo coupling reaction between the nitrene moiety with the coordinated isocyanide ligand to afford the **INT14** intermediate, which requires an energy barrier of 16.9 kcal/mol. Next, another substrate, $PhNH_2$, could undergo nucleophilic attack to the central carbon of **INT14**, leading to intermediate **INT16**. The formed **INT6** intermediate might dissociate from the Co(II) center after the ligand exchange step with the isocyanide. As discussed previously, the energy barriers for the subsequent conversion from **INT6** to the final product are not very high in the absence of the Co(II) catalyst, which suggests a facile process to occur. The catalytic role of the Co(II) catalyst in the conversion from **INT14** to the final product, if any, should not play a critical role. Overall, the catalytic role of Co(II) catalyst might attribute to promoting the dissociation of N_2 from the sulfonyl azide to yield the Co(III)-nitrene intermediate. In addition, the preference of the coordination of isocyanides to cobalt center would make the subsequent coupling reaction with the formed nitrene moiety ready to occur. The whole catalytic cycle was summarized in Scheme 8.

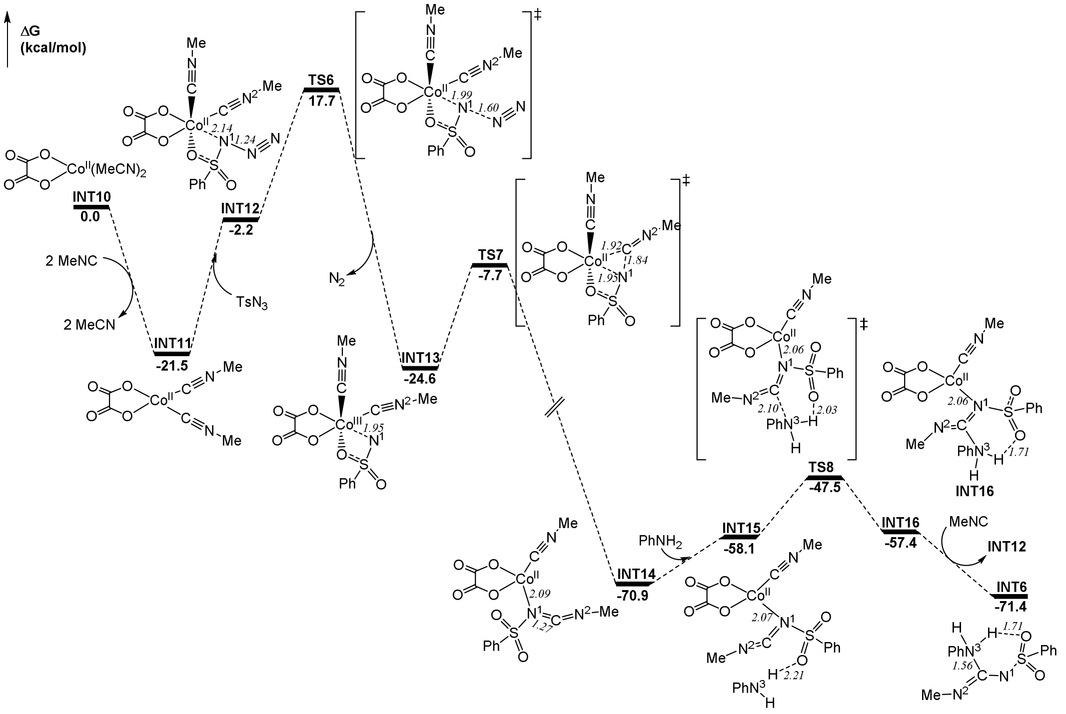


Figure 4. Energy profile (in kcal/mol) for the formation of the key Co(III)-nitrene intermediate and subsequent coupling reaction with the coordinated isocyanide ligand. Bond lengths are shown in Å.

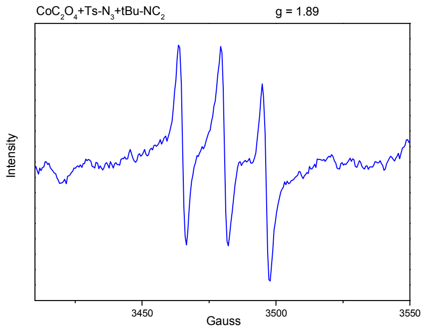
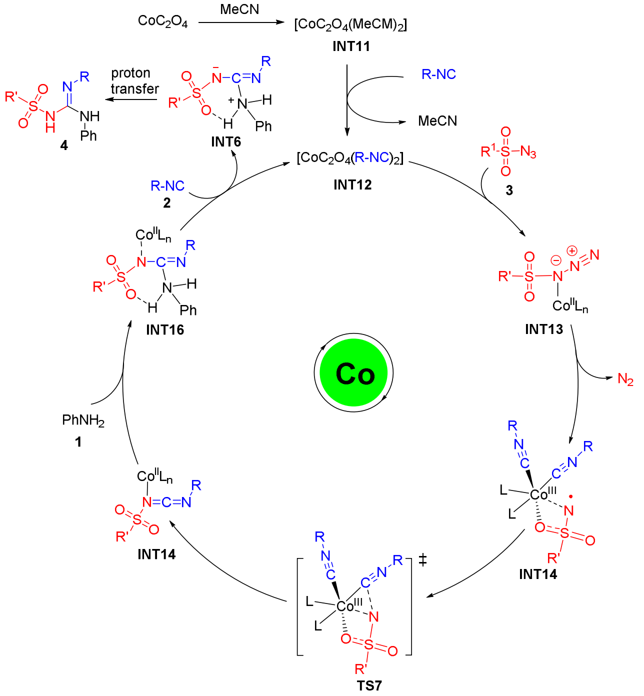


Figure 5. EPR spectra of ^{t}Bu-NC **2a** (0.5 mmol), Ts-N_3 **3a** (0.5 mmol), CoC_2O_4 (0.5 mmol) in MeCN (3 mL) at 298 K

To further confirm the formation of key Co(III)-nitrene intermediate, electron paramagnetic resonance (EPR) experiments were also carried out (Figure 5). We found that no EPR signal was observed when the mixture of CoC_2O_4 and *p*-toluenesulfonyl azide **3a** was tested. Following the isonitrile **2a** added, a strong triplet EPR signal was observed (g = 1.89) and the hyperfine coupling constant a^N = 15.47. We also found that the EPR signal was significantly attenuated after 48 h (More details of the EPR signals please see Supporting Information).

Scheme 8. Plausible Mechanism



■ CONCLUSION

In summary, we have developed a Co(II)-catalyzed synthesis of sulfonyl guanidines by using amines, isonitriles, and organic azides as nitrene source. This protocol provides an environmentally-friendly, and simple strategy for the synthesis of sulfonyl guanidine derivatives with a range of substrates and will find potential applications in organic synthesis. The catalytic role of Co(II) catalyst might attribute to promoting the dissociation of N_2 from the sulfonyl azide to generate the Co(III)-nitrene intermediate, which could be detected by EPR spectroscopy. In addition, the preference of the coordination of isocyanides to cobalt center would make the subsequent coupling reaction with the formed nitrene moiety ready to occur. Further investigations of the Co(II)-catalyzed nitrene reactions are currently under study in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Detailed experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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(17) Intersystem crossing (ISC) could occur to form the triplet ground state of the nitrene intermediate ^{3}**INT2** from the excited singlet state (^{1}**INT1**).

(18) A smaller isocyanide model, MeNC, was used in the computational study.

(19) The direct intramolecular proton transfer route for **INT6** to furnish the final product, however, has a relatively higher energy barrier (22.9 kcal/mol) compared with the intermolecular proton pathway assisted by another $PhNH_2$ molecule (see SI, Figure S2a). In addition, the intramolecular stepwise proton transfer to reach the final product was also considered, in which an H in the $PhNH_2$ moiety of **INT6** migrates to an O in the sulfonyl group first and subsequently transfers to N^1 to afford the final product (see SI, Figure S2b). However, the predicted energy barrier for this stepwise intramolecular proton transfer process is also higher (24.4 kcal/mol relative to **INT6**) than the intermolecular proton transfer pathway.

(20) The dissociation of N_2 using the model with one isocyanide and one sulfonyl azide was also studied. The predicted $\Delta G^‡$ is 19.5 kcal/mol, which is very close to that calculated based on **INT11**. See SI, Figure S3).