ORGANIC
LETTERS

2007
Vol. 9, No. 23
4889−4892

Cobalt-Catalyzed Intramolecular C–H Amination with Arylsulfonyl Azides

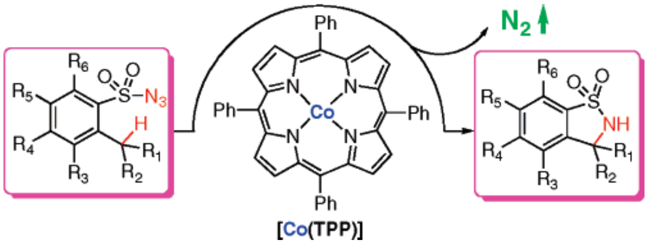
Joshua V. Ruppel, Rajesh M. Kamble, and X. Peter Zhang*

Department of Chemistry, University of South Florida, Tampa, Florida 33620-5250

pzhang@cas.usf.edu

Received September 16, 2007

ABSTRACT



Cobalt complexes of porphyrins are effective catalysts for intramolecular C–H amination with arylsulfonyl azides. The cobalt-catalyzed process can proceed efficiently under mild and neutral conditions in low catalyst loading without the need of other reagents or additives, generating nitrogen gas as the only byproduct. The catalytic system can be applied to primary, secondary, and tertiary C–H bonds and is suitable for a broad range of arylsulfonyl azides, leading to high-yielding syntheses of various benzosultams.

Metal-mediated nitrene transfer reactions are important chemical processes that allow the selective conversion of hydrocarbons to valuable nitrogen-containing compounds via direct C−N bond formation.[1,2] Using $\mathrm{PhI{=}NTs}$ and related iminoiodane derivatives as the primary nitrene sources, significant progress has been made in both catalytic aziridination of alkenes and amination of C−H bonds.[2−4] Great efforts have been made to overcome several limitations associated with the use of the hypervalent iodine reagents, which include their instability and the generation of ArI as a byproduct. While the approach of in situ iminoiodane generation in the presence of a terminal oxidant has met with enormous successes recently,[5,6] alternative nitrene sources such as chloramine-T,[4h,7] bromamine-T,[8] and tosyloxycarbamates[9] have been actively pursued to improve catalytic nitrene transfer reactions.

---

(1) (a) Racci, A., Ed. *Modern Amination Methods*; Wiley-VCH: Weinheim, 2000. (b) Salvatore, R. N.; Yoon, C. H.; Jung, K. W. *Tetrahedron* **2001**, *57*, 7785. (c) Johannsen, M.; Jorgensen, A. *Chem. Rev.* **1998**, *98*, 1689. (d) Muller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675.

(2) (a) Muller, P.; Fruit, V. *Chem. Rev.* **2003**, *103*, 2905. (b) Halfen, J. A. *Curr. Org. Chem.* **2005**, *9*, 657.

(3) (a) Dauban, P.; Dodd, R. H. *Synlett* **2003**, 1571. (b) Koser, G. F. *Top. Curr. Chem.* **2003**, *224*, 137.

(4) For representative examples of C-H amination with $\mathrm{ArI{=}NTs}$, see: (a) Mahy, J.-P.; Bedi, G.; Battioni, P.; Mansuy, D. *New J. Chem.* **1989**, *13*, 651. (b) Nageli, I.; Baud, C.; Bernardinelli, G.; Jacquier, Y.; Moran, M.; Muller, P. *Helv. Chim. Acta* **1997**, *80*, 1087. (c) Au, S.-M.; Huang, J.-S.; Che, C.-M.; Yu, W.-Y. *J. Org. Chem.* **2000**, *65*, 7858. (d) Yang, J.; Weinberg, R.; Breslow, R. *Chem. Commun.* **2000**, 531. (e) Yamawaki, M.; Tsutsui, H.; Kitagaki, S.; Anada, M.; Hashimoto, S. *Tetrahedron Lett.* **2002**, *43*, 9561. (f) Liang, J.-L.; Huang, J.-S.; Yu, X.-Q.; Zhu, N.; Che, C.-M. *Chem. Eur. J.* **2002**, *8*, 1563. (g) Cui, Y.; He, C. *J. Am. Chem. Soc.* **2003**, *125*, 16202. (h) Fructos, M. R.; Trofimenko, S.; Diaz-Requejo, M. M.; Perez, P. J. *J. Am. Chem. Soc.* **2006**, *128*, 11784. (i) Li, Z.; Capretto, D. A.; Rahaman, R.; He, C. *Angew. Chem., Int. Ed.* **2007**, *46*, 5184.

(5) For recent reviews, see: (a) Davies, H. M. L.; Long, M. S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3518. (b) Espino, C. G.; Du Bois, J. In *Modern Rhodium-Catalyzed Organic Reactions*; Evans, P. A., Ed.; Wiley-VCH; Weinheim, 2005; pp 379−416. (c) Davies, H. M. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 6422.

(6) For representative examples of in situ iminoiodane generation for catalytic nitrene transfers, see: (a) Yu, X.-Q.; Huang, J.-S.; Zhou, X.-G.; Che, C.-M. *Org. Lett.* **2000**, *2*, 2233. (b) Dauban, P.; Saniere, L.; Tarrade, A.; Dodd, R. H. *J. Am. Chem. Soc.* **2001**, *123*, 7707. (c) Espino, C. G.; Du Bois, J. *Angew. Chem., Int. Ed.* **2001**, *40*, 598. (d) Cui, Y.; He, C. *Angew. Chem., Int. Ed.* **2004**, *43*, 4210. (e) Li, Z.; Ding, X.; He, C. *J. Org. Chem.* **2006**, *71*, 5876. (f) Reddy, R. P.; Davies, H. M. L. *Org. Lett.* **2006**, *8*, 5013. (g) Liang, C.; Robert-Peillard, F.; Fruit, C.; Muller, P.; Dodd, R. H.; Dauban, P. *Angew. Chem., Int. Ed.* **2006**, *45*, 4641. (h) Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2007**, *129*, 562.

(7) (a) Simkhovich, L.; Gross, Z. *Tetrahedron Lett.* **2001**, *42*, 8089. (b) Albone, D. P.; Aujla, P. S.; Taylor, P. C.; Challenger, S.; Derrick, A. M. *J. Org. Chem.* **1998**, *63*, 9569. (c) Albone, D. P.; Challenger, S.; Derrick, A. M.; Fillery, S. M.; Irwin, J. L.; Parsons, C. M.; Takada, H.; Taylor, P. C.; Wilson, D. J. *Org. Biomol. Chem.* **2005**, *3*, 107.

10.1021/ol702265h CCC: $37.00

Azides represent a broad class of compounds that have the potential to be considered as ideal nitrene sources for metal-mediated nitrene transfer reactions.[10,11] In addition to their wide availability and ease of synthesis, azide-based nitrene transfers generate chemically stable and environmentally benign nitrogen gas as the only byproduct. Despite these attributes, only a few catalytic systems have been developed that can effectively catalyze the decomposition of azides for aziridination and amination.[11] Notable examples include Co(Por)-based amination with aryl azides[12] and Ru(Salen)-based aziridination with arylsulfonyl azides.[13,14]

In connection with our studies on the development of Co(Por)-catalyzed carbene transfer reactions with diazo reagents,[15,16] we recently reported a Co-based catalytic system that can catalyze olefin aziridination with the commercially available diphenylphosphoryl azide (DPPA) as a convenient new nitrene source, leading to the formation of *N*-phosphorylated aziridines with dinitrogen as the byproduct.[17] As part of our ongoing efforts to exploit the potential of azides for nitrene transfer reactions, herein we describe our results on Co-catalyzed intramolecular C−H amination with azides. Commercially available Co(TPP) (Figure 1) was shown to be an effective catalyst for intramolecular nitrene insertion of C−H bonds with a broad range of arylsulfonyl azides (**1**),[18] leading to the high-yielding syntheses of the corresponding benzosultam derivatives (**2**) (Scheme 1), which have been found in various important applications.[19] The Co-catalyzed process proceeded efficiently under mild and neutral conditions in low catalyst loading without the need of other reagents or additives, while generating dinitrogen as the only byproduct.

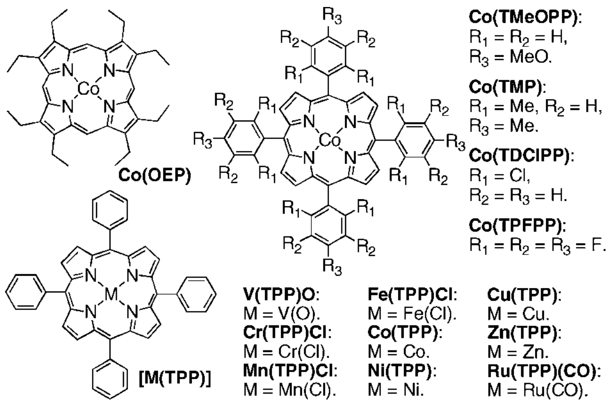
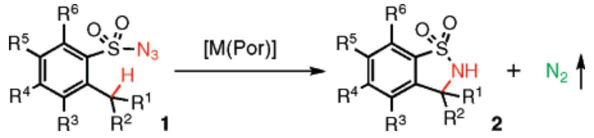


Figure 1. Structures of metalloporphyrin catalysts.

Scheme 1. Catalytic Intramolecular C−H Amination of Arylsulfonyl Azides



Using the commercially available 2,4,6-triisopropylbenzenesulfonyl azide (**1a**) as a model substrate, we first surveyed potential catalytic activity of various metalloporphyrins (Figure 1) toward intramolecular C−H amination (Table 1). The reactions were carried out with 2 mol % of metalloporphyrin at 80 °C overnight in chlorobenzene, which was identified previously as the solvent of choice for aziridination with DPPA.[17] It was evident that Co(II) was by far the most active metal ion for the intramolecular C−H amination with TPP as the supporting ligand, forming the desired benzosultam **2a** in 96% yield (Table 1, entry 5). While the V(IV), Cr(III), Mn(III), Ni(II), Cu(II), and Zn(II) complexes produced no or only trace amounts of **2a** (Table 1, entries 1−3 and 6−8), Fe(TPP)Cl and Ru(TPP)(CO) could

---

(8) (a) Chanda, B. M.; Vyas, R.; Bedekar, A. V. *J. Org. Chem.* **2001**, *66*, 30. (b) Vyas, R.; Gao, G.-Y.; Harden, J. D.; Zhang, X. P. *Org. Lett.* **2004**, *6*, 1907. (c) Gao, G.-Y.; Harden, J. D.; Zhang, X. P. *Org. Lett.* **2005**, *7*, 3191. (d) Harden, J. D.; Ruppel, J. V.; Gao, G.-Y.; Zhang, X. P. *Chem. Commun.* **2007**. Published online: http://dx.doi.org/10.1039/b710677g.

(9) (a) Lebel, H.; Huard, K.; Lectard, S. *J. Am. Chem. Soc.* **2005**, *127*, 14198. (b) Lebel, H.; Leogane, O.; Huard, K.; Lectard, S. *Pure Appl. Chem.* **2006**, *78*, 363. (c) Lebel, H.; Huard, K. *Org. Lett.* **2007**, *9*, 639.

(10) (a) Scriven, E. F. V.; Turnbull, K. *Chem. Rev.* **1988**, *88*, 297. (b) Brase, S.; Gil, C.; Knepper, K.; Zimmermann, V. *Angew. Chem., Int. Ed.* **2005**, *44*, 5188.

(11) (a) Katsuki, T. *Chem. Lett.* **2005**, 1304. (b) Cenini, S.; Gallo, E.; Caselli, A.; Ragaini, F.; Fantauzzi, S.; Piangiolino, C. *Coord. Chem. Rev.* **2006**, *250*, 1234.

(12) (a) Cenini, S.; Gallo, E.; Penoni, A.; Ragaini, F.; Tollari, S. *Chem. Commun.* **2000**, 2265. (b) Ragaini, F.; Penoni, A.; Gallo, E.; Tollari, S.; Gotti, C. L.; Lapadula, M.; Mangioni, E.; Cenini, S. *Chem. Eur. J.* **2003**, *9*, 249.

(13) (a) Omura, K.; Murakami, M.; Uchida, T.; Irie, R.; Katsuki, T. *Chem. Lett.* **2003**, 354. (b) Omura, K.; Uchida, T.; Irie, R.; Katsuki, T. *Chem. Commun.* **2004**, 2060.

(14) While this manuscript was in the process of submission, Driver and co-workers reported a formal arene C−H insertion reaction of vinyl azides catalyzed by dimeric rhodium perfluorobutyrate, see: Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500.

(15) (a) Huang, L.; Chen, Y.; Gao, G.-Y.; Zhang, X. P. *J. Org. Chem.* **2003**, *68*, 8179. (b) Lee, M.-Y.; Chen, Y.; Zhang, X. P. *Organometallics* **2003**, *22*, 4905. (c) Chen, Y.; Fields, K. B.; Zhang, X. P. *J. Am. Chem. Soc.* **2004**, *126*, 14718. (d) Chen, Y.; Zhang, X. P. *J. Org. Chem.* **2007**, *72*, 5931. (e) Chen, Y.; Ruppel, J. V.; Zhang, X. P. *J. Am. Chem. Soc.* **2007**, *129*, 12074.

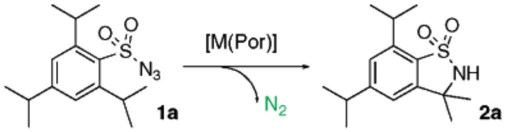
(16) For [Co(Por)]-catalyzed cyclopropanation, see: Penoni, A.; Wanke, R.; Tollari, S.; Gallo, E.; Musella, D.; Ragaini, F.; Demartin, F.; Cenini, S. *Eur. J. Inorg. Chem.* **2003**, 1452.

(17) Gao, G.-Y.; Jones, J. E.; Vyas, R.; Harden, J. D.; Zhang, X. P. *J. Org. Chem.* **2006**, *71*, 6655.

(18) Careful control experiments showed the arylsulfonyl azides reported in this work were stable under the conditions used, but it should be noted that some of the azide compounds may be explosive and should be handled with great care.

(19) Among various important applications, benzosultams have been demonstrated as versatile chiral auxiliaries, novel HIV-1 reverse transcriptase inhibitors, and potential COX-2 inhibitors. For selected examples, see: (a) Elgazwy, A.-S. S. H. *Tetrahedron* **2003**, *59*, 7445. (b) Lee, A. W. M.; Chan, W. H.; Zhang, S.-J.; Zhang, H.-K. *Curr. Org. Chem.* **2007**, *11*, 213. (c) Zaharevitz, D. W.; Gusio, R.; Wiegand, A.; Jailuri, R.; Pattabiraman, N.; Kellogg, G. E.; Pallansch, L. A.; Yanf, S. S.; Buckheit, R. W., Jr. *Med. Chem. Res.* **1999**, *9*, 551. (d) Headrick, S. A. Ph.D. Dissertation. University of Tennessee, Knoxville, TN, U.S.A., 2003. (e) Baker, D. C.; Jiang, B. U.S. Patent 6,353,112 B1, 2002. (f) Mao, J.; Baker, D. C. U.S. Patent 6,458,962 B1, 2002. (g) Baker, D. C.; Mayasundari, A.; Mao, J.; Johnson, S. C.; Yan, S. U.S. Patent 6,562,850 B1, 2003. (h) Singh, S. K.; Reddy, P. G.; Rao, K. S.; Lohray, B. B.; Misra, P.; Rajjak, S. A.; Rao, Y. K.; Venkateswarlu, A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 499. (i) Pal, M.; Veeramaneni, V. R.; Kumar, S.; Vangoori, A.; Mullangi, R.; Misra, P.; Rajjak, S. A.; Lohray, V. B.; Casturi, S. R.; Yeleswarapu, K. R. *Lett. Drug Design Discovery* **2005**, *2*, 329.

Table 1. Intramolecular Nitrene C−H Bond Insertion of 2,4,6-Triisopropylbenzenesulfonyl Azide Catalyzed by Metalloporphyrins[a]



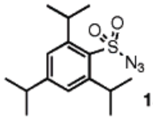
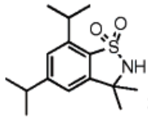
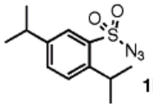
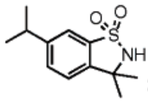
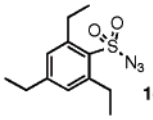
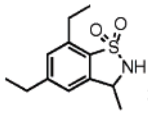
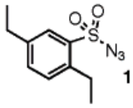
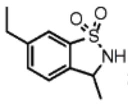
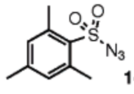
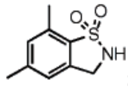
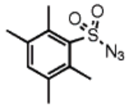
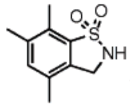
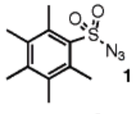
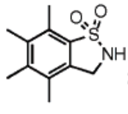
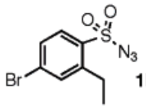
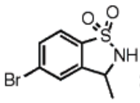
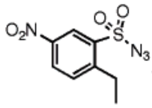
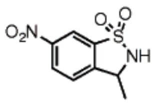
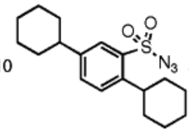
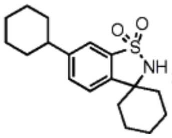
entry	[M(Por)][b]	mol (%)[c]	solvent	temp (°C)	yield (%)[d]
1	V(TPP)O	2.0	C_6H_5Cl	80	0
2	Cr(TPP)Cl	2.0	C_6H_5Cl	80	0
3	Mn(TPP)Cl	2.0	C_6H_5Cl	80	<5[e]
4	Fe(TPP)Cl	2.0	C_6H_5Cl	80	11
5	Co(TPP)	2.0	C_6H_5Cl	80	96
6	Ni(TPP)	2.0	C_6H_5Cl	80	0
7	Cu(TPP)	2.0	C_6H_5Cl	80	0
8	Zn(TPP)	2.0	C_6H_5Cl	80	0
9	Ru(TPP)(CO)	2.0	C_6H_5Cl	80	67
10	Co(OEP)	2.0	C_6H_5Cl	80	86
11	Co(TMeOPP)	2.0	C_6H_5Cl	80	93
12	Co(TMP)	2.0	C_6H_5Cl	80	30
13	Co(TPFPP)	2.0	C_6H_5Cl	80	8
14	Co(TDClPP)	2.0	C_6H_5Cl	80	5
15	Co(TPP)	2.0	C_6H_5Cl	40	95
16	Co(TPP)	2.0	C_6H_5Cl	23	91
17	Co(TPP)	2.0	CH_2Cl_2	23	91
18	Co(TPP)	2.0	$C_6H_5CH_3$	23	85
19	Co(TPP)	0.5	C_6H_5Cl	80	88
20	Co(TPP)	0.5	C_6H_5Cl	80	92[f]
21	----	0.0	C_6H_5Cl	80	0

[a] Performed for 18 h under N_2 in the presence of 5 Å molecular sieves with **[1a]** = 0.20 M. [b] See Figure 1 for structures. [c] Catalyst loading. [d] Isolated yields. [e] Estimated yield. [f] Carried out for 42 h.

also catalyze the reaction to produce **2a** in 11% and 67% yield, respectively (Table 1, entries 4 and 9). Control experiments showed that no reaction was observed in the absence of a catalyst (Table 1, entry 21). After the superiority of Co ion was established, several common porphyrins with different electronic and steric properties were applied to probe the ligand effect (Figure 1). While both Co(OEP) and Co(TMeOPP) could effectively catalyze the reaction (Table 1, entries 10 and 11), an increase in ligand steric hindrance and/or electron deficiency resulted in poor catalytic activity (Table 1, entries 12−14). The Co(TPP)-catalyzed reaction could also proceed well at lower and even room temperatures (Table 1, entries 15 and 16) and in different solvents (Table 1, entries 17 and 18). A decrease in catalyst loading to 0.5 mol % had no dramatic effect on the catalytic process (Table 1, entries 19 and 20).

The Co(TPP)-based catalytic system was found to be suitable for a broad range of arylsulfonyl azides (Table 2), which were readily prepared from the corresponding aryl compounds (Supporting Information). For each arylsulfonyl azide substrate, the catalytic reactions were evaluated at three different temperatures: 80 °C, 40 °C, and room temperature. In addition to intramolecular nitrene insertion into tertiary C−H bonds in **1a** and **1b** (Table 2, entries 1−2), secondary (Table 2, entries 3−4), and even primary (Table 2, entries 5−7) C−H bonds having various aromatic substitution patterns can be effectively aminated as well, resulting in selective formation of the corresponding five-membered heterocycles. Although they all could be intramolecularly inserted in excellent yields at 80 °C, the reactivity seemed to follow in the order of 3° > 2° > 1° C−H bonds. The difference in their reactivities became more noticeable when the reactions were conducted at lower temperatures (Table 2, entries 1−5). It is interesting to note that an increase in substitution on the aromatic ring led to higher-yielding formation of the amination products (Table 2, entries 5−7), suggesting a positive buttressing effect of meta and para groups on the nitrene insertion of ortho C−H bonds.

Table 2. [Co(TPP)]-Catalyzed Intramolecular C−H Amination[a]

entry	azide	sultam	temp (°C)	yield (%)[b]
1	 **1a**	 **2a**	80 40 23	96 95 91
2	 **1b**	 **2b**	80 40 23	94 82 72
3	 **1c**	 **2c**	80 40 23	90 54 19
4	 **1d**	 **2d**	80 40 23	91 57 40
5	 **1e**	 **2e**	80 40 23	96 32 18
6	 **1f**	 **2f**	80 40 23	91 58 37
7	 **1g**	 **2g**	80 40 23	95 79 47
8	 **1h**	 **2h**	80 40 23	93 77 46
9	 **1i**	 **2i**	80 40 23	99 85 69
10	 **1j**	 **2j**	80 40 23	87 33 23

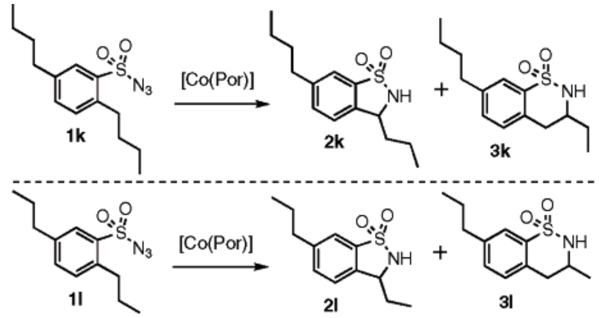
[a] Performed in C_6H_5Cl for 18 h under N_2 with 2 mol % [Co(TPP)] in the presence of 5 Å MS; [azide] = 0.20 M. [b] Isolated yields.

Arylsulfonyl azides containing functional groups such as bromo and nitro at different positions could also be successfully catalyzed (Table 2, entries 8−9).

The aforementioned reactivity order of 3° > 2° > 1° C−H bonds, perhaps in combination with the higher reactivity of benzylic C−H bonds, resulted in exclusive formation of five-membered ring structures in all the above cases where 1° and 3° or 1° and 2° C−H bonds coexist in the substrates (Table 2, entries 1−4 and 8−9). Azide **1j** represents a case that contains both 2° and 3° C−H bonds (Table 2, entry 10). As in the other cases (Table 2, entries 1−4 and 8−9), the exclusive high-yielding formation of five-membered spiroheterocyclic product was observed as a result of the reactivity order of 3° > 2° > 1° C−H bonds.

When an azide substrate containing different 2° C−H bonds such as benzylic and non-benzylic types was employed, however, both five- and six-membered ring formations were observed. For example, Co(TPP)-catalyzed intramolecular C−H amination of azide **1k** with an *n*-butyl group led to the production of six-membered **3k** as well as the five-membered **2k** (Table 3, entries 1−3). The ratio of **2k** to **3k** was determined to be 72:28, 68:32, and 67:33 at 80 °C, 40 °C, and room temperature, respectively. The increase in the ratio of **2k** to **3k** at elevated temperature suggests the higher thermodynamic stability of the five-membered ring structure. When **1l** with an *n*-propyl group was used, both the five-membered **2l** and six-membered **3l** were similarly formed (Table 3, entries 4−6). The ratio of five- to six-membered ring products, which was 56:44, 56:44, and 54:46 at 80 °C, 40 °C, and room temperature, respectively, however, was significantly lower than the those of azide **1k** reactions. Our preliminary results indicated that the ratio of five- to six-membered ring formations could be influenced with the use of different porphyrin ligands. While a similar ratio of **2l** to **3l** was obtained for Co(TMP)- or Co(TMeOPP)-catalyzed reactions (Table 3, entries 7 and 8), the ratio was significantly increased to 73:27 when Co(OEP) was used as the catalyst (Table 3, entry 9).

Table 3. Five- and Six-Membered Ring Formations via Intramolecular C−H Amination Catalyzed by Cobalt Porphyrins[a]



entry	azide	[Co(Por)][b]	temp (°C)	sultam	distribution[c]	yield (%)[d]
1	**1k**	Co(TPP)	80	**2k** + **3K**	72 + 28	91
2	**1k**	Co(TPP)	40	**2k** + **3K**	68 + 32	41
3	**1k**	Co(TPP)	23	**2k** + **3K**	67 + 33	25
4	**1l**	Co(TPP)	80	**2l** + **3l**	56 + 44	94
5	**1l**	Co(TPP)	40	**2l** + **3l**	56 + 44	56
6	**1l**	Co(TPP)	23	**2l** + **3l**	54 + 46	33
7	**1l**	Co(TMP)	80	**2l** + **3l**	55 + 45	77
8	**1l**	Co(TMeOPP)	80	**2l** + **3l**	59 + 41	97
9	**1l**	Co(OEP)	80	**2l** + **3l**	73 + 27	92

[a] Performed in C_6H_5Cl for 18 h under N_2 with 2 mol % [Co(Por)] in the presence of 5 Å MS; [azide] = 0.20 M. [b] See Figure 1 for structures. [c] Ratio of 5- to 6-membered ring products determined by NMR; see SI for details. [d] Combined isolated yields of 5- and 6-membered ring products; see SI for details.

In summary, we have developed the first Co-based catalytic system for intramolecular C−H amination with azides. We demonstrated that the commercially available Co(TPP) is an effective and general catalyst for catalyzing intramolecular C−H amination with arylsulfonyl azides, leading to the valuable benzosultam derivatives in excellent yields.[19] In addition to 1°, 2°, and 3° benzylic C−H bonds, non-benzylic C−H bonds can also be intramolecularly aminated. Continuous efforts are underway to identify suitable catalysts with high regioselectivity toward either five- or six-membered ring formation. Further studies are required to render the Co-based catalytic system stereoselective by employing chiral porphyrin ligands with desired electronic, steric, and chiral environments.[15c]

Acknowledgment. We are grateful for financial support of this work from USF for Startup Funds, American Chemical Society for a PRF-AC grant, and the National Science Foundation for a CAREER Award. Funding for the USF Department of Chemistry Mass Spectrometry Facility has been furnished in part by NSF (CRIF:MU-0443611).

Supporting Information Available: Analytical data and NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

OL702265H