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Cobalt(II)-Catalyzed Intramolecular C−H Amination with Phosphoryl Azides: Formation of 6- and 7-Membered Cyclophosphoramidates

Hongjian Lu, Jingran Tao, Jess E. Jones, Lukasz Wojtas, and X. Peter Zhang*

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

pzhang@cas.usf.edu

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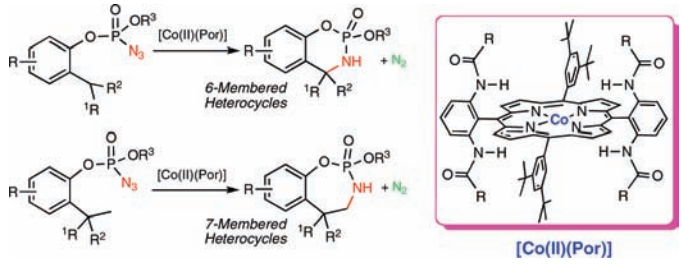
ABSTRACT



A highly effective Co(II)-based system has been developed for catalytic intramolecular C−H amination with phosphoryl azides without the need of terminal oxidant or other additives, resulting in the high-yielding production of cyclophosphoramidates with nitrogen gas as the byproduct. Additional features of this new catalytic system include the amination of primary C−H bonds and formation of 7-membered-ring structures.

Metal-catalyzed C−H amination via nitrene insertion constitutes a general strategy for the direct functionalization of C−H bonds with potential control of selectivities.[1] The past decade has witnessed enormous progress in intramolecular C−H amination, as a direct result of the successful employment of dimeric $Rh(II)_2$-based catalysts in combination of various types of iminoiodane nitrene sources that can be generated in situ with terminal oxidants.[2] Notable examples include $Rh(II)_2$-catalyzed intramolecular oxidative C−H amination of carbamates and sulfamates, generating synthetically valuable 5- and 6-membered heterocycles, respectively.[1−3] In addition to substrate design, the continued success of this potentially far-reaching catalytic approach demands further development of effective metal catalysts as well as suitable nitrene sources.

As a broad class of compounds that can be readily accessed via straightforward synthesis, azides have the potential to serve as a general type of alternative nitrene source for metal-catalyzed C−H amination.[4] In addition to their wide availability, amination processes with azides can proceed under neutral conditions without the need of a terminal oxidant or

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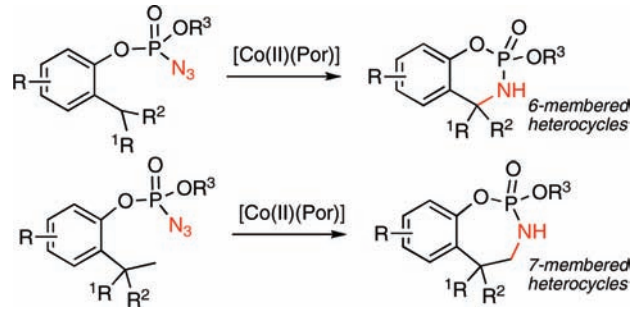
base, while generating nitrogen gas as the only byproduct.[5] In spite of these potential advantages, only a few metal complexes have been recognized as effective catalysts for the decomposition of azides for C−H amination.[6−9] They include the recently reported intermolecular (Co/aryl[6] and carbonyl[7a] azides; Cu/adamantyl azide[8]) and intramolecular (Co/arylsulfonyl azide;[7b] Rh_2/vinyl[9a] and aryl[9b] azides) systems.

Phosphoryl azides represent a common class of compounds[10] and have been previously employed by Breslow and co-workers to generate phosphoryl nitrenes via photolysis for studying photochemical reactions.[11] It was shown that the resulting phosphoryl nitrenes were so intriguingly nonselective that they underwent intermolecular C−H amination with the solvents without the normal preference for intramolecular reactions.[11] While Rh_2Piv_4 was indicated to catalyze the intramolecular C−H amination, the catalytic thermolysis appeared to be ineffective (52% yield with 15% catalyst at 120 °C for 87 h).[11b] We report herein that Co(II) complexes of appropriate porphyrins [Co(Por)] are highly effective catalysts for intramolecular C−H amination with phosphoryl azides under mild conditions.[12] Determined by the nature of the azides, the Co(II)-based catalytic system can undergo 1,6- or 1,7-C−H nitrene insertion processes, forming O−P−N containing 6- or 7-membered benzoheterocyclic compounds in high yields (Scheme 1). Cyclophosphoramidates and related heterocycles have found a number of applications, in particular in the fields of catalysis and medicine.[13] For example, the 1,3,2-oxazaphosphinane ring system exists in anticancer drugs cyclophosphamide and ifosfamide (Figure 1).[13e,g] In addition to secondary and tertiary C−H bonds, the current catalytic system is featured with effective amination of both benzylic and nonbenzylic primary C−H bonds.

Scheme 1. Co(II)-Catalyzed Intramolecular 1,6- and 1,7-C−H Nitrene Insertion Processes with Phosphoryl Azides



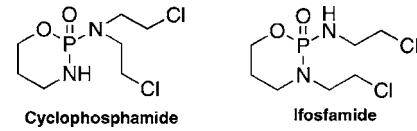


Figure 1. 1,3,2-Oxazaphosphinane ring-based anticancer drugs.

Using phosphoryl azide **1a** as a model substrate, we performed a systematic investigation of its potential catalytic intramolecular C−H amination reactivity utilizing Co(II) complexes of different porphyrins under various conditions (Table 1 and Table S1 in the Supporting Information). As summarized in Table 1, the commercially available [Co(TPP)] (TPP: tetraphenylporphyrin), which was demonstrated previously to be effective in catalyzing both intermolecular C−H amination of carbonyl azides[7a] and intramolecular C−H amination of arylsulfonyl azides,[7b] was unproductive for the amination of **1a** (Table 1, entry 1), indicating phosphoryl azides have lower reactivity than carbonyl and sulfonyl azides. Encouraged by the hydrogen-bonding-enhanced catalysis observed in the previous aziridination system,[14] [Co(**P1**)], in which the D_{2h}-symmetric porphyrin **P1** has amide functionalities at the *ortho*-positions of the *meso*-phenyl groups, was employed as a potential catalyst and was indeed found to successfully catalyze formation of the desired amination product **2a** in 79% yield (Table 1, entry 2). This suggests possible hydrogen-bonding interaction between the P═O and N−H units in the supposed nitrene intermediate (Figure S1, Supporting Information).[14] Consistent with this depiction, the use of [Co(**P2**)] and [Co(**P3**)],

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(10) For example, the commercially available, low cost diphenylphosphoryl azide (DPPA) is a stable and distillable liquid that has been widely used in organic syntheses. For early examples, see: (a) Shioiri, T.; Ninomiya, K.; Yamada, S. *J. Am. Chem. Soc.* **1972**, *94*, 6203. (b) Yamada, S.; Ikota, N.; Shioiri, T.; Tachibana, S. *J. Am. Chem. Soc.* **1975**, *97*, 7174.

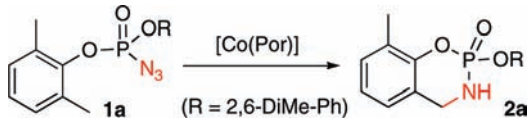
(11) (a) Breslow, R.; Feiring, A.; Herman, F. *J. Am. Chem. Soc.* **1974**, *96*, 5937. (b) Breslow, R.; Herman, F.; Schwabacher, A. W. *J. Am. Chem. Soc.* **1984**, *106*, 5359. (c) Maslak, P. *J. Am. Chem. Soc.* **1989**, *111*, 8201. (d) Maslak, P.; Sczepanski, J. J.; Minard, R. D.; Collins, L. A. *Tetrahedron Lett.* **1990**, *31*, 4261.

(12) For the use of DPPA in catalytic aziridination, see: (a) Gao, G.-Y.; Jones, J. E.; Vyas, R.; Harden, J. D.; Zhang, X. P. *J. Org. Chem.* **2006**, *71*, 6655. (b) Jones, J. E.; Ruppel, J. V.; Gao, G.-Y.; Moore, T. M.; Zhang, X. P. *J. Org. Chem.* **2008**, *73*, 7260.

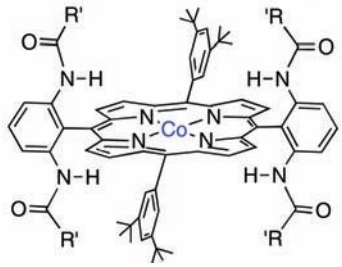
(13) (a) Denmark, S. E.; Beutner, G. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 1560. (b) Minnaard, A. J.; Feringa, B. L.; Lefort, L.; de Vries, J. G. *Acc. Chem. Res.* **2007**, *40*, 1267. (c) Frank, E.; Wolfling, J. *Curr. Org. Chem.* **2007**, *11*, 1610. (d) Jiang, Y.; Han, J.; Yu, C.; Vass, S. O.; Searle, P. F.; Browne, P.; Knox, R. J.; Hu, L. *J. Med. Chem.* **2006**, *49*, 4333. (e) Kivela, H.; Zalan, Z.; Tahtinen, P.; Sillanpaa, R; Fulop, F.; Phihlaja, K. *Eur. J. Org. Chem.* **2005**, 1189. (f) Caminade, A.-M.; Majorai, J. P. *Chem. Rev.* **1994**, *94*, 1183. (g) Brock, N. *Cancer Res.* **1989**, *49*, 1. (h) Pankiewicz, K.; Kinas, R.; Stec, W. J.; Foster, A. B.; Jarman, M.; Van Maanen, M. S. *J. Am. Chem. Soc.* **1979**, *101*, 7712. (i) Eto, M.; Kinoshita, Y.; Kato, T.; Oshima, Y. *Nature* **1963**, *200*, 171. (j) Arnold, H.; Bourseaux, F.; Brock, N. *Nature* **1958**, *181*, 931.

(14) (a) Ruppel, J. V.; Jones, J. E.; Huff, C. A.; Kamble, R. M.; Chen, Y.; Zhang, X. P. *Org. Lett.* **2008**, *10*, 1995. (b) Subbarayan, V.; Ruppel, J. V.; Zhu, S.-F.; Perman, J. A.; Zhang, X. P. *Chem. Commun.* **2009**, 4266.

Table 1. Intramolecular Nitrene C−H Bond Insertion of Phosphoryl Azide **1a** Catalyzed by Co(II) Complexes of Different Porphyrins[a]



entry	[Co(Por)]	yield (%)[b]	entry	[Co(Por)]	yield (%)[b]
1	[Co(TPP)][c]	0%	4	[Co(**P3**)]	96%
2	[Co(**P1**)]	79%	5	[Co(**P4**)]	<5%[d]
3	[Co(**P2**)]	98%	6	[Co(**P5**)]	0%



R' = *i*-Pr: [Co(**P1**)]
(**P1**: 3,5-Di^{t}Bu-IbuPhyrin)
R' = Me: [Co(**P2**)]
(**P2**: 3,5-Di^{t}Bu-AcePhyrin)
R' = Et: [Co(**P3**)]
(**P3**: 3,5-Di^{t}Bu-ProPhyrin)
R' = *t*-Bu: [Co(**P4**)]
(**P4**: 3,5-Di^{t}Bu-PivPhyrin)
R' = Ph: [Co(**P5**)]
(**P5**: 3,5-Di^{t}Bu-PhePhyrin)

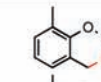
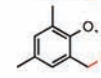
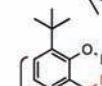
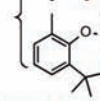
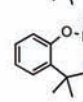
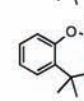
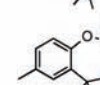
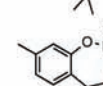
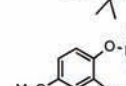
[a] Performed with 2 mol % of [Co(Por)] for 12 h in $PhCF_3$ at 80 °C under N_2 in the presence of 4 Å MS; [**1a**] = 0.10 M. [b] Isolated yields. [c] TPP = tetraphenylporphyrin. [d] Trace amount product.

which have less steric amide functionalities, increased the yields of **2a** to 98% and 96%, respectively (Table 1, entries 3 and 4). Conversely, **2a** was only produced in a trace amount or not formed at all when [Co(**P4**)] or [Co(**P5**)] was used (Table 1, entries 5 and 6), presumably due to the weakening or prohibition of the hydrogen-bonding interaction resulting from the steric hindrance of the bulky amides.

Under an optimized condition (1−2 mol % of [Co(**P2**)] at 80 °C in $PhCF_3$ for 24 h), the Co(II)-based catalytic system was found to be effective for the intramolecular C−H amination with a range of phosphoryl azides (Table 2).[15] For example, the primary C−H bonds of both azides **1a** and **1b** could be intramolecularly aminated, producing the 6-membered cyclophosphoramides **2a** and **2b**, respectively, in excellent yields (Table 2; entries 1 and 3). With a slightly higher catalyst loading (2 mol %), it was noted that the reactions could be catalyzed in equally high yields by [Co(**P1**)] (Table 2; entries 2 and 4). As anticipated, tertiary and secondary C−H bonds of various types were also suitable substrates for the catalytic system, forming the desired 6-membered heterocycles as a mixture of *trans*- and *cis*-isomers (Table 2; entries 5−9). The selective formation of **2e** from **1e** without amination of the primary C−H bonds and aziridination of the C=C double bond (Table 2; entry 7) indicates that the catalytic system may allow for high control of chemoselectivity. When azide **1h** was used as the substrate, it was a surprise to observe the formation of

(15) DSC experiments indicated that these phosphoryl azides were stable without decomposition up to at least 250 °C; see the Supporting Information for details.

Table 2. Co(II)-Catalyzed Intramolecular C−H Amination To Form 6- and 7-Membered Cyclophosphoramidates from Azides[a]

entry	azide	R	cyclophosphoramidate	yield (%)[b]
1	 **1a**		 **2a**	99
2				94[d]
3	 **1b**		 **2b**	92
4				99[d]
5	 **1c**	Et	 **2c**	94[c,d,f,g]
6	 **1d**	Et	 **2d**	90[c,d,h]
7	 **1e**		 **2e**	74[c,e,i]
8	 **1f**		 **2f**	83[c,e,j]
9	 **1g**		 **2g**	85[e]
10	 **1h**		 **2ha**	90%[d] **2ha**/**2hb** = 84/16
11			 **2hb**	96%[e] **2ha**/**2hb** = 76/24
12	 **1i**		 **2i**	96
13	 **1j**		 **2j**	55
14				85[e]
15				97[d]
16	 **1k**	Et	 **2k**	37
17				95[d]
18	 **1l**		 **2l**	99
19	 **1m**		 **2m**	99
20	 **1n**		**2n**	97
21	**1o**		**2o**	80[d,k]
22	**1p**	Et	**2p**	70[d,k]

[a] Performed with 1 mol % of [Co(**P2**)] for 24 h in $PhCF_3$ at 80 °C under N_2 in the presence of 4 Å MS; [**1**] = 0.10 M. [b] Isolated yields. [c] NMR yields. [d] 2 mol % of [Co(**P1**)]. [e] 2 mol % of [Co(**P2**)]. [f] 60 °C. [g] dr: 65/35. [h] dr: 55/45. [i] dr: 53/47. [j] dr: 91/9. [k] Partial decomposition during purification; yield would be higher.

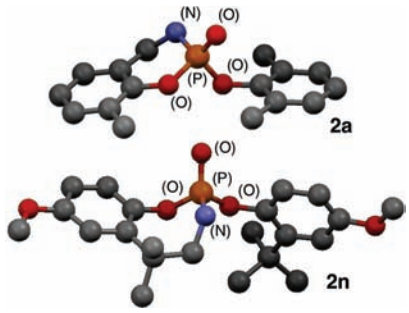


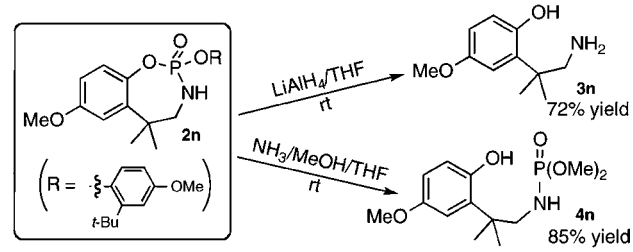
Figure 2. X-ray crystal structures of 6-membered (**2a**) and 7-membered (**2n**) cyclophosphoramidates.

7-membered **2hb** in addition to the major 6-membered **2ha** (Table 2; entries 10 and 11), suggesting the unusual capability of the current catalytic system for the amination of both benzylic and nonbenzylic primary C−H bonds as well as for the construction of medium-sized ring structures. It was shown subsequently that various 7-membered cyclophosphoramidates could be cleanly generated in high yields in the absence of benzylic C−H bonds as exemplified with azides **1i**−**p** that contain different functional groups (Table 2; entries 12−22).

Besides various spectroscopic characterizations, both the 6-membered (**2a**) and 7-membered (**2n**) O−P−N containing benzoheterocyclic structures were further confirmed by X-ray crystallographic analysis (Figure 2).

In addition to their various applications shown in the literature,[13] these cyclophosphoramidates should also serve as useful precursors for preparation of synthetically valuable 1,3- and 1,4-amino alcohols. As an example to demonstrate this kind of synthetic utility, the phosphoryl group of 7-membered amination product **2n** could be fully deprotected upon treatment with $LiAlH_4$ in THF at room temperature, generating 1,4-amino alcohol **3n** in 72% isolated yield (Scheme 2). By changing reaction conditions, partial deprotection of the phosphoryl group also was found to be possible. When **2n** in THF was treated with a solution of NH_3/MeOH at room temperature, the *N*-protected 1,4-amino alcohol **4n** was isolated in 85% yield as a result of controlled double methanolysis of the phosphoryl diester without affecting the phosphoryl amide linkage.

Scheme 2. Preparation of Amino Alcohol and *N*-Protected Amino Alcohol via Full and Partial Deprotection of Phosphoryl Groups



In summary, a Co(II)-based catalytic system has been established for the highly effective intramolecular C−H amination of phosphoryl azides,[15] producing a wide range of cyclophosphoramidates in high yields with nitrogen gas as the only byproduct. In addition to its neutral and nonoxidative conditions, this new catalytic system is highlighted with features such as amination of primary C−H bonds and formation of 7-membered-ring structures. Further studies are underway to render the catalytic system stereoselective.

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Supporting Information Available: Experimental procedures and analytical data for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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