Cyclization

DOI: 10.1002/ange.201400557

Chemoselective Amination of Propargylic C(sp^3)–H Bonds by Cobalt(II)-Based Metalloradical Catalysis**

Hongjian Lu, Chaoqun Li, Huiling Jiang, Christopher L. Lizardi, and X. Peter Zhang**

Abstract: *Highly chemoselective intramolecular amination of propargylic C(sp^3)–H bonds has been demonstrated for N-bishomopropargylic sulfamoyl azides through cobalt(II)-based metalloradical catalysis. Supported by D_{2h}-symmetric amidoporphyrin ligand 3,5-Di^{t}Bu-IbuPhyrin, the cobalt(II)-catalyzed C–H amination proceeds effectively under neutral and nonoxidative conditions without the need of any additives, and generates N_2 as the only byproduct. The metalloradical amination is suitable for both secondary and tertiary propargylic C–H substrates with an unusually high degree of functional-group tolerance, thus providing a direct method for high-yielding synthesis of functionalized propargylamine derivatives.*

Significant effort has been devoted to developing synthetic methods for accessing propargylamines as they serve as versatile intermediates in organic synthesis,[1] as well as important structural elements in natural and synthetic products having interesting biological activities.[2] Traditionally, propargylamines have been prepared through the addition of metal alkynylides to imines. Since this traditional method typically requires stoichiometric amounts of metal alkynylides, which are known to be moisture sensitive,[3] it reduces the degree of functional-group tolerance and has largely restricted the applications. Consequently, there has been continued interest in developing new methods for the synthesis of propargylamines under mild reaction conditions with a high degree of functional-group tolerance. Among the different approaches that have been developed recently, the transition-metal-catalyzed three-component one-pot coupling of an aldehyde, an alkyne, and an amine represents one of the most general and atom-economic methods. This so-called A^3-coupling provides a catalytic method for efficient synthesis of propargylamines under mild reaction conditions with H_2O as the only byproduct.[4,5] Since A^3-coupling is mainly suitable for aldehydes as one of the coupling partners, its application has been limited to the preparation of propargylamines bearing a tertiary carbon center at the propargylic position.[6]

Selective amination of omnipresent C–H bonds by metal-mediated nitrene insertion represents a powerful approach for direct introduction of valuable amino functionalities into molecules.[7] This direct transformation has the potential to serve as an efficient alternative to traditional approaches for amine syntheses, which are based on functional-group transformations. Its realization may have far-reaching impact for amine synthesis and their practical applications in different fields. Accordingly, the direct synthesis of propargylamines based on metal-catalyzed amination of propargylic C–H bonds could become an alternative approach to traditional methods. In addition to propargylamines containing tertiary carbon atoms, catalytic propargylic C–H amination would also allow preparation of propargylamines bearing a quaternary carbon center at the propargylic position. While metal-catalyzed amination has been successfully demonstrated with several different types of C–H substrates,[7] few catalytic systems are known for chemoselective amination of propargylic C(sp^3)–H bonds.[8a,9] Because of the electrophilic nature of the key metallonitrene intermediates, its addition to more-electron-rich C≡C bonds would be typically preferred over amination of the propargylic C–H σ bonds.[8] By decreasing the electrophilicity of the corresponding Rh_2/nitrene intermediates through replacement of the sulfamates with carbamates, Schomaker and co-workers reported that intramolecular propargylic C–H amination of homopropargylic carbamates could be successfully catalyzed by [Rh_2(esp)$_2$] in combination with PhI(OAc)$_2$ and MgO, thus generating five-membered propargylamine derivatives in good yields.[9a] However, because of the competitive electrophilic addition of Rh_2/nitrene intermediates to the electron-rich C≡C bonds under these catalytic conditions,[8a] the intramolecular propargylic C–H amination of sulfamates gave the corresponding six-membered propargylamines in only moderate yields.[8a,9a] It should be noted that the ring size of the resulting heterocycles from intramolecular C–H amination is typically governed by the substrate geometry and lengths of the tethers.[7a]

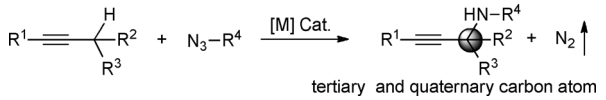
Cobalt(II) complexes of porphyrins, [Co(Por)], which exist as stable metalloradicals, have emerged as a new class of catalysts which have proven to be effective for activating azides as nitrene sources for amination of various types of C–H bonds, including challenging primary and electron-deficient C–H bonds.[10,11] Different from electrophilic metallonitrene intermediates associated with Rh_2-catalyzed systems, the cobalt(II)-based metalloradical amination has been demonstrated to proceed through a stepwise radical mecha-

[*] Prof. Dr. H. J. Lu, Dr. C. Li, Dr. H. Jiang, C. L. Lizardi, Prof. Dr. X. P. Zhang
Department of Chemistry, University of South Florida
Tampa, FL 33620-5250 (USA)
E-mail: xpzhang@usf.edu
Prof. Dr. H. J. Lu
Institute of Chemistry and BioMedical Sciences
School of Chemistry and Chemical Engineering
Nanjing University, Nanjing, 210093 (China)
E-mail: hongjianlu@nju.edu.cn

[**] We are grateful for financial support from the NSF (CHE-1152767) and NIH (R01-GM098777).

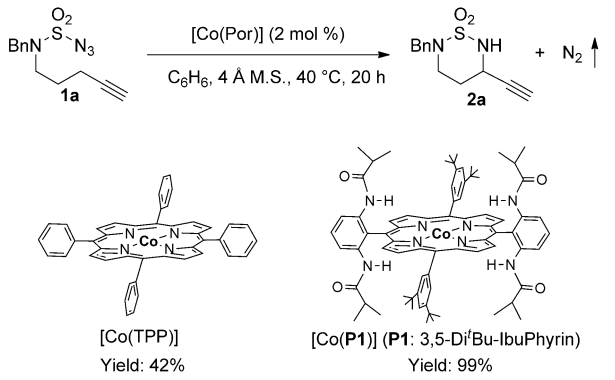
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/anie.201400557.

nism.[12] Consequently, it has been shown that the reactivity and selectivity profile of the cobalt(II)-based amination system is governed by the bond dissociation energy (BDE) rather than electron density of the reacting C–H bonds.[11a–c] This concept of metalloradical catalysis (MRC) has been successfully applied to address chemoselectivity issues in intramolecular allylic C–H amination versus competitive C=C aziridination.[11b] Considering the fact that the BDE of secondary propargylic C–H bonds is similar to that of secondary allylic C–H bonds ($\approx$83 kcal mol^{-1}),[13] we anticipated the possibility of chemoselective amination of propargylic C–H bonds through cobalt(II)-based MRC if the radical addition of the cobalt(II)/nitrene radical to C≡C bonds could be disfavored. Herein, we report that [Co(Por)] catalysts are effective for intramolecular amination of sulfamoyl azides with complete control of the chemoselectivity for propargylic C–H bonds without direct reaction at the C≡C bond or other common C–H bonds (Scheme 1).



Scheme 1. Synthesis of propargylamines by catalytic C–H amination.

At the onset of our study, the *N*-bishomopropargylic sulfamoyl azide **1a**[14,15] was used as the initial substrate for intramolecular C–H amination by [Co(Por)] (Scheme 2). We were delighted to find that intramolecular amination of the secondary propargylic C–H α to the unprotected terminal alkyne in **1a** was catalyzed by [Co(TPP)] (2 mol% at 40°C), thus forming the corresponding propargylamine **2a** in a moderate yield (42%). The catalytic reaction exhibited complete chemoselectivity toward propargylic C–H amination, without competitive homopropargylic C–H amination and addition to the C≡C bond. When [Co(**P1**)], in which the D_{2h}-symmetric porphyrin ligand 3,5-Di^{t}Bu-IbuPhyrin **P1** is functionalized with amide functionalities, as hydrogen-bonding donors, at the *ortho*-positions of the *meso*-phenyl groups,[16] was used as the catalyst, the yield for chemoselective formation of **2a** was dramatically improved to near quantitative. This result represents another demonstration of hydrogen-bonding

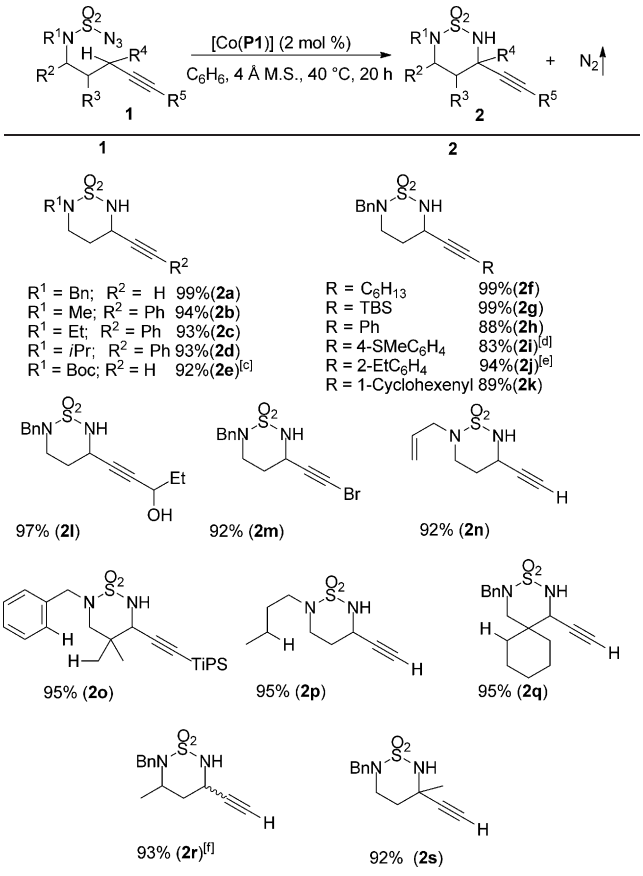


Scheme 2. Ligand effects on the [Co(Por)]-catalyzed intramolecular propargylic C–H amination of sulfamoyl azide. M.S. = molecular sieves.

acceleration in a cobalt(II)-based MRC.[11a–e] It is worth emphasizing the operational simplicity and cleanness of the cobalt(II)/azide-based system, which gave rise to a catalytic process where the desired product **2a** existed as the sole compound after completion of the reaction.

Under the optimized reaction conditions (2 mol% of [Co(**P1**)] in benzene at 40°C for 20 h), the intramolecular propargylic amination was shown to be applicable to the sulfamoyl azides **1** having various *N* substitutions (Table 1). For example, the substrates containing electron-donating *N*-alkyl substituents, whose corresponding sulfamides would be degraded under the $[Rh_2(esp)_2]$/PhI(OAc)$_2$/MgO catalytic system,[17] were suitable substrates for the cobalt(II)-based metalloradical system, as shown by the chemoselective C–H amination reactions of sulfamoyl azides with *N*-benzyl (**2a**), *N*-methyl (**2b**), *N*-ethyl (**2c**), *N*-isopropyl (**2d**), *N*-allyl (**2n**), and *N*-butyl (**2p**) substituents. Additionally, the propargylic C–H bonds in sulfamoyl azides with electron-withdrawing *N* substituents were also successfully aminated with complete chemoselectivity, as exemplified by the high-yielding forma-

Table 1: Synthesis of functionalized propargylamine derivatives from chemoselective propargylic C–H amination of sulfamoyl azides catalyzed by [Co(**P1**)].[a,b]



[a] Performed in C_6H_6 at 40°C for 20 h using 2 mol% [Co(**P1**)] under N_2 in the presence of 4 Å M.S.; [azide **1**] = 0.10 M. [b] Yield of isolated products. [c] 5 mol% [Co(**P1**)], azide **1e** = 1.0 mmol. [d] 80°C for 3 h. [e] Yield of isolated products after repeating the reaction three times without isolating the catalyst. [f] d.r. = 68:32. Boc = *tert*-butoxycarbonyl, TBS = *tert*-butyldimethylsilyl, TIPS = triisopropylsilyl.

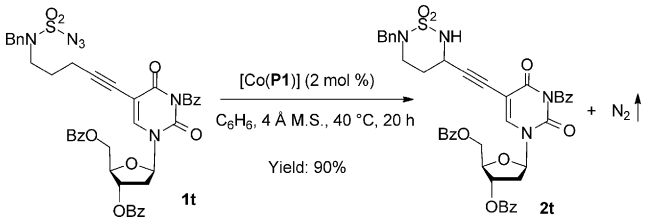
tion of the six-membered propargylamine **2e** from the corresponding *N*-Boc-protected azide on a 1.0 mmol scale. This result indicates that the radical reactivity of the corresponding cobalt(III)/nitrene radical intermediate remained the dominant factor despite its increased electrophilicity owing to the presence of the electron-withdrawing *N* substituent.

Moreover, the cobalt(II)-catalyzed chemoselective C–H amination could be applied to a wide range of sulfamoyl azides bearing different alkyne elements (Table 1). In addition to the azides with terminal alkynes (**2a**, **2e**, **2n**, and **2p**–**s**), the catalytic system was also suitable for azides derived from internal alkynes with various substituents, as demonstrated by the high-yielding amination reactions of alkynes substituted with aryl (**2b**–**d** and **2h**–**j**), alkyl (**2f** and **2l**), and silyl (**2g** and **2o**) groups. It should be noted that the sulfide group in the azide **1i** was well tolerated because of the non-oxidative conditions. Furthermore, intramolecular propargylic C–H amination of the enyne-based sulfamoyl azide **1k** could also be chemoselectively catalyzed by [Co(**P1**)], thus forming the propargylamine **2k** without affecting the conjugated enyne functionality. The high degree of functional-group tolerance and chemoselectivity of the cobalt(II)-based metalloradical system was further demonstrated with the amination of the sulfamoyl azide **1l** containing an unprotected propargylic secondary alcohol; remarkably, the catalytic reaction afforded the desired propargylic amine **2l** in excellent yield without any side reactions from the propargylic alcohol unit. It is noted that the intramolecular C–H amination of the corresponding carbamate with the similar propargylic alcohol unit was shown to be problematic for the Rh_2-based catalytic system.[9] Surprisingly, the cobalt(II)-catalyzed system could be extended to the 1-bromoalkyne-derived sulfamoyl azide **1m**, thus forming the corresponding amination product **2m** in a high yield with no complication from the bromoethynyl functional group. The outstanding chemoselectivity toward propargylic C–H amination was further highlighted by the catalytic reactions of the sulfamoyl azide **1n** with an *N*-allyl substituent. Despite the existence of both alkene and alkyne functionalities, which are normally prone to electrophilic addition, [Co(**P1**)] chemoselectively aminated the propargylic C–H bond without affecting the potentially reactive C=C and C≡C bonds. The multifunctional propargylic amine products such as **2k**–**n** may serve as intermediates for the synthesis of other useful amine derivatives. For example, **2l** may allow access to the corresponding allenic amine, which is difficult to prepare.[9a] In addition to chemoselectivity, our preliminary results also demonstrated the possibility of controlling the enantioselectivity of the C–H amination process through the employment of cobalt(II) complexes of D_2-symmetric chiral amidoporphyrins [Co(D_2-Por*)] as chiral metalloradical catalysts (see Table S1 in the Supporting Information).[18] Furthermore, to enhance the practicality of the catalytic system, the amination reaction of azide **1j** was successfully repeated three times without isolating the catalyst [Co(**P1**)], thus affording the desired product **2j** in similarly high yields (see Table S2 in the Supporting Information).

The BDEs were recognized as a fundamentally important factor in metalloradical amination for controlling and differentiating reactivity and selectivity of various C–H bonds.[11] This governing principle was also well demonstrated in the current catalytic system, [Co(**P1**)], for regioselective amination of the propargylic C–H bonds of sulfamoyl azides (Table 1). Previous reports indicated that the normal aliphatic C–H bonds, including primary, secondary, and tertiary C(sp^3)–H bonds, could also be effectively aminated by [Co(**P1**)] under similar reaction conditions.[11a] As a result of the lower BDE of propargylic C–H bonds (BDE of propargylic C–H bonds: ca. 85 kcal mol^{-1}; BDE of aliphatic C–H bonds: ca. 98 kcal mol^{-1}),[13] we showed that the intramolecular amination of propargylic C–H bonds could be selectively catalyzed by [Co(**P1**)] in the presence of different types of aliphatic C–H bonds (Table 1). Using the *N*-benzyl-*N*-bishomopropargylic sulfamoyl azide **1o** as an example, the cobalt(II)-based metalloradical system achieved the highly selective 1,6-amination of the propargylic C–H bonds in **1o** without amination of the much stronger primary C(sp^3)–H bonds and aromatic C(sp^2)–H bonds located the same number of carbon atoms away. Similarly, highly regioselective propargylic amination was accomplished in the presence of acyclic and cyclic secondary C(sp^3)–H bonds, as shown with the catalytic reactions of **1p** and **1q**, respectively.

In addition to the above examples of various sulfamoyl azides with secondary propargylic C–H bonds for formation of propargylamines containing a tertiary carbon atom, the cobalt(II)-catalyzed 1,6-C–H amination process worked equally well with tertiary propargylic C–H substrates, as illustrated by the effective amination reaction of the sulfamoyl azide **1s**, which gave the corresponding propargylamine **2s** containing a synthetically challenging quaternary carbon center in 92% yield (Table 1).[19]

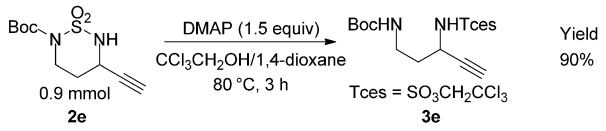
This cobalt(II)-based MRC intramolecular propargylic C–H amination presents a practical route to access various unsymmetric cyclic sulfamide derivatives (**2**). In view of the impressively diverse array of biological activities of cyclic sulfamide-containing compounds reported in numerous recent patents,[20] the products **2**, bearing other functionalities in addition to the highly versatile alkyne functional groups, may serve as valuable synthetic intermediates for applications in biology and medicine. Furthermore, the neutral and non-oxidative reaction conditions of the cobalt(II)-based catalytic system may allow direct use of substrates which have pharmaceutical relevance and often contain various functionalities. For example, the [Co(**P1**)] catalyst could be successfully utilized for intramolecular amination of the deoxyuridine-based substrate **1t**, thus providing the new deoxyuridine derivative containing the cyclic sulfamide **2t** in 90% yield (Scheme 3). When the reaction was scaled up to 0.65 mmol and with a lower catalyst loading (0.5 mol%), a similarly high yield (88%) was obtained in 70 hours. Given that the variants of deoxyuridine, such as idoxuridine and trifluridine, have been used as antiviral drugs,[21] this type of modification of deoxyuridine may offer an attractive opportunity for obtaining new compounds having interesting biological activities. Such a high degree of functional-group tolerance exhibited by



Scheme 3. Application of catalytic propargylic C–H amination for deoxyuridine-based sulfamoyl azide. Bz = benzoyl.

cobalt(II)-based MRC should increases the potential of this catalytic system for synthetic applications.

As another exploration of their synthetic applications, the products **2** could serve as convenient precursors for the synthetically valuable 1,3-diamines. For example, the -SO_2- bridging unit in **2e** could be conveniently opened on a 0.9 mmol scale by alcohols such as 2,2,2-trichloroethanol in the presence of DMAP,[17] thus providing the corresponding alkyne-containing 1,3-diamine **3e** in a high yield (Scheme 4).



Scheme 4. Ring-opening reaction for the generation of 1,3-propargylic diamine with different protecting groups. DMAP = 4-(*N*,*N*-dimethylamino)pyridine

Since the two amine units in **3e** are differentially protected by Boc and Tces groups, it should be easily transformed into various 1,3-diamine derivatives by utilizing known transformations for alkynes.

In summary, we have demonstrated for the first time a chemoselective catalytic system using cobalt(II)-based metalloradical catalysis for intramolecular amination of propargylic C(sp^3)–H bonds of *N*-bishomopropargylic sulfamoyl azides. The metalloradical catalyst [Co(**P1**)] is highly effective for chemoselective amination of different types of propargylic C–H bonds with excellent regioselectivity, thus affording six-membered cyclic sulfamides, with unaffected alkyne substituents, in excellent yields.[22] In addition to the alkyne functionality, the cobalt(II)-based metalloradical amination, which operates under neutral and non-oxidative conditions, has been shown to tolerate a range of other functional groups, including alkenes and unprotected alcohols. The resulting tertiary and quaternary carbon-containing propargylamine products from this new catalytic process may find a myriad of synthetic applications.

Received: January 18, 2014
Revised: March 16, 2014
Published online: May 19, 2014

Keywords: alkynes · chemoselectivity · cobalt · heterocycles · homogeneous catalysis

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[22] Efforts are on the way to expand the application of the cobalt(II)-based amination system for formation of five- and seven-membered cyclic sulfamides as well as sulfamates.

