ORGANIC LETTERS

2012
Vol. 14, No. 19
5158–5161

Stereoselective Radical Amination of Electron-Deficient C(sp^3)−H Bonds by Co(II)-Based Metalloradical Catalysis: Direct Synthesis of α-Amino Acid Derivatives via α-C−H Amination

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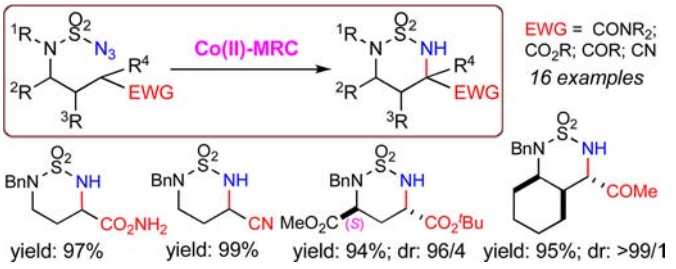
Received September 12, 2012

ABSTRACT



The cobalt(II) complex of 3,5-Di^{t}Bu-IbuPhyrin, [Co(P1)], is an effective catalyst for intramolecular amination of electron-deficient C−H bonds, including those adjacent to electron-withdrawing CO_2R, $C(O)NR_2$, C(O)R, and CN groups, in excellent yields with high regio- and stereoselectivity. The [Co(P1)]-catalyzed amination system provides a direct method for the synthesis of α-amino acid derivatives from the corresponding carboxylate precursors.

Nitrogen-containing compounds are of central importance in biology and medicine.[1] The development of synthetic methodologies that allow for selective conversion of omnipresent C−H bonds into valuable amine functional groups promises to transform the art and practice of organic synthesis and should lead to many new applications. Among several approaches, catalytic C−H amination via metal-mediated nitrene insertion represents one of the most general and direct methods for installation of amino functionalities with potential control of various selectivities. Research efforts in this direction have been exceedingly prolific and have led to the development of a number of C−H amination systems based on different combinations of metal catalysts and nitrene sources.[2] Represented by dirhodium(II) tetracarboxylate catalysts in conjunction with *in situ* generated iminoiodane nitrene sources, existing catalytic systems have enabled effective amination of benzylic, allylic, and other electron-rich C−H bonds with high regio- and stereoselectivity.[2] The potential of catalytic amination, however, has not been fully extended to other types of more challenging C−H bonds, especially the electron-deficient C−H bonds due to their incompatibility with electrophilic metallonitrene intermediates intervened in most current catalytic systems.

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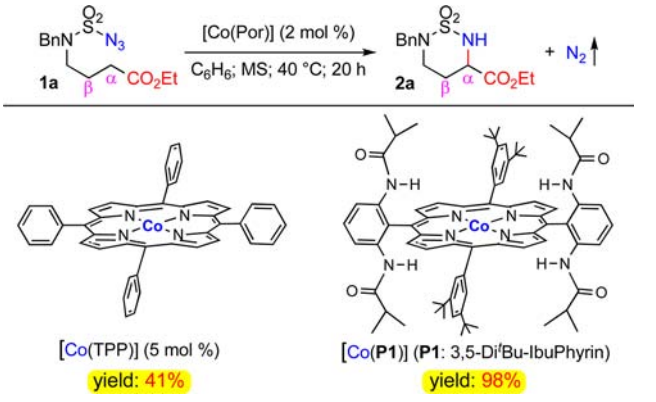
10.1021/ol302511f
Published on Web 09/21/2012

The C−H bonds in the α-position of electron-withdrawing groups such as esters, amides, ketones, and nitriles are the common electron-deficient C−H bonds that have not been successfully demonstrated for metal-catalyzed amination. Clearly, this mode of transformation would be highly desirable because α-C−H amination of esters and amides may offer a direct method for stereoselective synthesis of biologically important α-amino acid derivatives.[3] To the best of our knowledge, the only previous report that briefly touched the subject is the Rh_2-catalyzed intramolecular α-C−H amination of *N*-Boc-protected sulfamide esters.[4,5] Evidently, amination of electron-deficient C−H bonds is an unaddressed issue that faces formidable challenges in both reactivity and regioselectivity.

Cobalt(II) porphyrins, a family of stable metalloradicals with well-defined open-shell doublet d^7 electronic structure, have recently arisen as a new class of catalysts for selective C−H amination.[6] These Co(II)-based metalloradical catalysts have proven to be unusually effective on the activation of various organic azides, including sulfonyl,[7] phosphoryl,[8] carbonyl,[9] and aryl[10] azides, for amination of broad classes of C−H bonds under neutral and nonoxidative conditions.[11] Particularly, Co(II) complexes of D_{2h}-symmetric amidoporphyrins [Co(D_{2h}-Por)] have revealed an uncommon catalytic capacity for efficient intramolecular amination of strong primary C−H bonds[7b,8] and have also displayed excellent chemoselectivity for intramolecular allylic C−H amination over the competitive C=C aziridination.[7c] Several lines of experimental and computational evidence back the radical mechanism of Co(II)/azide-based C−H amination that involves an unusual Co(III)-nitrene radical intermediate undergoing a stepwise radical abstraction−substitution pathway.[7b,c,12,13] Considering the nonelectrophilic nature of this radical mechanism, which is fundamentally different from the electrophilic metallonitrene mechanism shared by the widely studied Rh_2 and other closed-shell systems, we envisaged the possibility of addressing the aforementioned challenge of intramolecular electron-deficient C−H amination through Co(II)-based metalloradical catalysis.

Scheme 1. Ligand Effect on Intramolecular Amination of Electron-Deficient C−H Bonds by Co(II) Porphyrins



At the onset of our investigation, we evaluated the catalytic intramolecular C−H amination reaction of *N*-benzyl sulfamoyl azide **1a**,[14,15] which contains electron-deficient secondary C−H bonds positioned α to the ester unit, by Co(II) porphyrins (Scheme 1). Under the typical neutral and nonoxidative conditions of Co(II)-based metalloradical catalysis, we were thrilled to find that even the simple [Co(TPP)] was capable of aminating the electron-deficient secondary α-C−H bonds in **1a** to form the corresponding six-membered cyclic sulfamide-based amino acid ester **2a** despite the fact that a relatively higher catalyst loading (5 mol %) was employed. Although the yield was moderate (41%), the α-C−H amination was very clean without observation of β-C−H amination, indicative of its slow reaction rate. When the Co(II) complex of D_{2h}-symmetric amidoporphyrin 3,5-Di^{t}BuIbuPhyin [Co(**P1**)] was employed as the catalyst,[7b,c,8] the amination rate was drastically enhanced to afford the desired amino acid derivative **2a** in 98% yield in spite of a lower catalyst loading (2 mol %). This ligand-enhanced catalysis is presumably contributed to the cooperative hydrogen bonding interaction between the groups S=O of the substrate and N−H of the catalyst.[13a,16]

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(13) For related DFT studies on the radical mechanism of Co(Por)]-catalyzed olefin aziridination, see: (a) Suarez, A. I. O.; Jiang, H. L.; Zhang, X. P.; de Bruin, B. *Dalton Trans.* **2011**, *40*, 5697. (b) Hopmann, K. H.; Ghosh, A. *ACS Catal.* **2011**, *1*, 597.

(14) Sulfamoyl azides were reported to be chemically stable, even in strong acidic and basic conditions (see ref 15). Our DSC experiments indicated that these sulfamoyl azides were thermally stable without decomposition up to at least 100 °C; see Supporting Information for a representative DSC plot of azide **1a**.

(15) (a) Griffith, J. *J. Chem. Soc. C* **1971**, 3191. (b) Goddard-Borger, E. D.; Stick, R. V. *Org. Lett.* **2007**, *9*, 3797.

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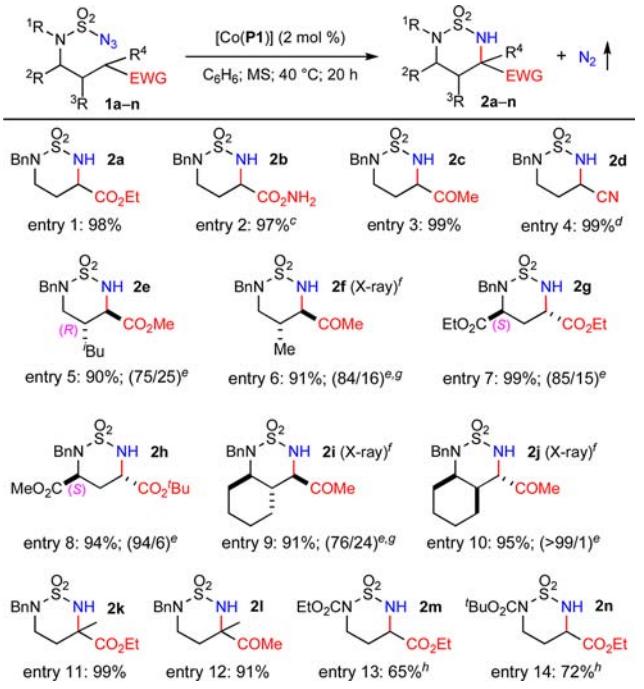
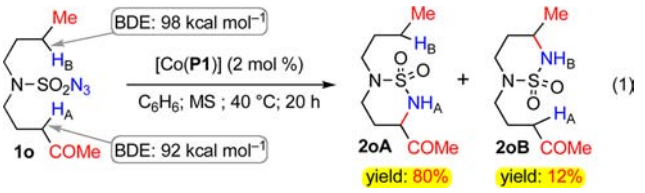
Scheme 2. Regio- and Stereoselective Intramolecular Amination of Electron-Deficient C−H Bonds by [Co(**P1**)][a,b]

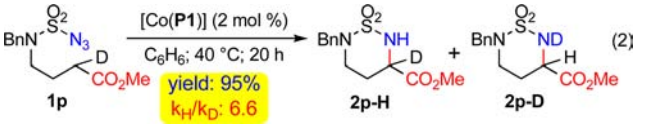


[a] [**1**] = 0.10 M. [b] Isolated yields. [c] 4 mol % [Co(**P1**)]. [d] 80 °C for 3 h. [e] Diastereomeric ratios determined by ^{1}H NMR. [f] Confirmed by X-ray crystallographic structure analysis. [g] Purity of azides: 93−95%. [h] 5 mol % of [Co(**P1**)] at 80 °C for 1 h .

The [Co(**P1**)]-catalyzed intramolecular amination was found to be generally effective for various types of electron-deficient C−H bonds (Scheme 2). In addition to the α-C−H bonds of the ester **1a** (entry 1), the Co(II)-based system could efficiently catalyze α-C−H amination of amides, ketones, and nitriles as demonstrated with reactions of azides **1b**−**1d**, respectively, affording the desired amination products **2b**−**2d** in excellent yields (entries 2−4). Its complete regioselectivity toward 1,6-amination of electron-deficient C−H bonds was further highlighted by the high-yielding diastereoselective reactions of the *β*-substituted azides **1e**−**1f** without any interference from 1,5- or 1,6-amination of the electron-rich C−H bonds (entries 5−6). Higher to excellent diastereoselectivities were achieved for regioselective α-C−H amination of enantiopure *γ*-substituted azide esters **1g**−**1h**, affording optically active bis-α-amino acid derivatives **2g**−**2h** in high yields (entries 7−8), which is in stark contrast to the Rh_2-catalyzed amination.[4] Furthermore, *β*,*γ*-disubstituted substrates such as cyclohexane-based *cis*- and *trans*-azide ketones **1i**−**1j** could be diastereoselectively aminated to produce the 6,6-bicyclic structures **2i**−**2j** in high yields (entries 9−10). As expected, the [Co(**P1**)]-catalyzed amination could be well applied to electron-deficient tertiary C−H bonds as exemplified with azide ester **1k** and azide ketone **1l**, resulting in high-yielding formation of α,α-disubstituted α-amino acid and ketone **2k** and **2l**, respectively (entries 11−12). In addition to *N*-benzyl-substituted substrates, the [Co(**P1**)]-catalyzed amination has been shown to be compatible with sulfamoyl azides having varied *N*-substitutions including oxidizable functional groups.[7b,c] Relatively slower reaction rates, however, were noticed for azide substrates that contain *N*-electron-withdrawing groups as shown with azides **1m** and **1n** (entries 13−14).



To shed some light on the origin of the remarkable catalytic capacity of the Co(II)-based system toward selective amination of electron-deficient C−H bonds, we performed a direct competition experiment between electron-deficient and -rich secondary C−H bonds with similar steric environments by choosing *N*-*n*-butyl sulfamoyl azide ketone **1o** as the amination substrate (eq 1). Under the standard catalysis of [Co(**P1**)], the reaction of **1o** afforded two products **2oA** and **2oB** in 80% and 12% yields, respectively, indicating that 1,6-amination of electron-deficient C−H_A was considerably faster than that of electron-rich C−H_B. This seemingly very surprising result can be rationalized on the basis of the stepwise radical abstraction−substitution mechanism of the Co(II)-catalyzed C−H amination.[7b,c,12,13] Since the C−H_A bond (92 kcal mol^{-1}) is significantly weaker than the C−H_B bond (98 kcal mol^{-1}),[17] the H-atom abstraction by the key Co(III)-nitrene radical intermediate is expected to be more facile for H_A than H_B.



Additional support for the participation of an H-atom transfer (HAT) key step in the radical mechanism of the Co(II)-based metalloradical amination was obtained through the measurement of kinetic isotope effect (KIE) (eq 2). When sulfamoyl azide ester **1p**, in which one of two α-H-atoms is replaced with a deuterium atom, was subjected to the standard catalytic conditions by [Co(**P1**)], the high-yielding reaction generated a mixture of two α-amino acid esters **2p-H** and **2p-D**, which resulted from α-C−H and α-C−D amination, respectively, of the monodeuterated substrate. Analysis of the product mixture by ^{1}H NMR provided an intramolecular KIE of 6.6. This degree of primary KIE, which is substantially greater than the determined value of 1.9 for Rh_2-catalyzed intramolecular amination of benzylic C−H bonds,[18] is comparable to that measured for Co(II)-based metalloradical allylic C−H amination,[7c] indicating the involvement of direct C−H

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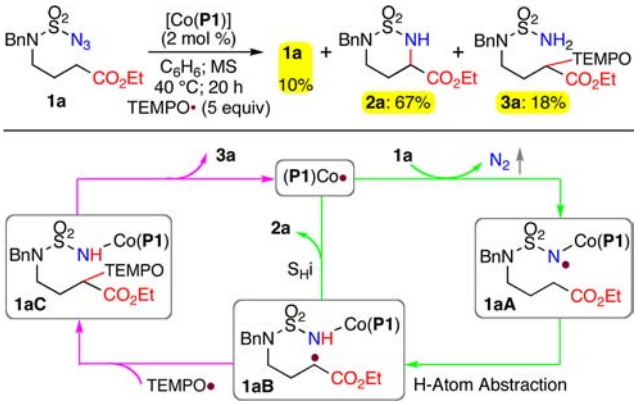
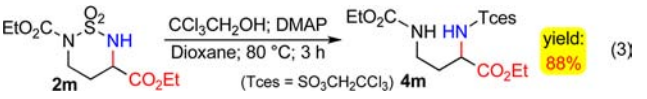
bond rupture via the HAT process by the key Co(III)-nitrene radical intermediate.[7b,c,12,13]

Scheme 3. TEMPO Trapping of Carbon-Based Radical Intermediate Involved in Radical Mechanism of Co(II)-Based Metalloradical C−H Amination



In an effort to trap the resulting carbon-based radical after H-atom abstraction by the Co(III)-nitrene radical intermediate, we carried out catalytic intramolecular C−H amination of azide ester **1a** by [Co(**P1**)] in the presence of stable oxygen-based radical TEMPO (Scheme 3). Addition of substoichiometric amounts of TEMPO was found to have no significant effect on the catalytic reaction as previously observed for Co(II)-catalyzed intramolecular allylic C−H amination.[7c] This observation, which seems to be abnormal for a catalytic reaction involved with radical intermediates, is actually consistent with the very low barrier (or barrierless) of the subsequent intramolecular homolytic substitution (S_Hi) step suggested by the DFT calculations of related catalytic systems.[12,13] When the amount of added TEMPO was increased to 5 equiv, however, the conversion of **1a** was decreased to 90% with 10% of the starting azide **1a** remaining under the same catalytic conditions (Scheme 3). While the α-amino acid ester **2a** was still formed as the major product in 67% yield, the reaction generated a new product **3a** in 18% yield. Detailed characterizations revealed **3a** as a TEMPO-containing sulfamide in which the TEMPO unit is attached to the α-position of the ester group via C−O bond formation. As illustrated in Scheme 3, the production of **3a** was likely originated from the intermediate **1aC** that was formed from TEMPO trapping of the C-based radical intermediate **1aB**. Presumably due to steric reasons, the initially generated Co(III)-nitrene radical intermediate **1aA** could undergo the HAT process to generate **1aB** without being affected by the presence of TEMPO. Together with the competition experiment and kinetic isotope effect, we take these results as new experimental evidence for the stepwise radical abstraction−substitution mechanism of the Co(II)-based metalloradical C−H amination.[7b,c,12,13]

Due to their stereogenic centers that are substituted with important functionalities such as ester, amide, ketone, and nitrile groups, the family of six-membered cyclic sulfamides constructed through Co(II)-catalyzed intramolecular α-amination of electron-deficient C−H bonds may find useful applications as intermediates for stereoselective synthesis, in addition to their known biomedical applications as potential inhibitors of several important enzymes.[19] In particular, the resulting cyclic sulfamide esters and amides are the direct precursors for the synthesis of α,γ-diamino acid derivatives upon removal of the SO_2 unit. As a demonstration of this aspect of application, cyclic sulfamide ester **2m** could be effectively converted to α,γ-diamino acid ester **4m** in 88% yield when it was treated with CCl_3CH_2OH in the presence of DMAP (eq 3).[4] Since the α- and γ-amine groups in **4m** are differentially protected, its further transformations should provide access to various α,γ-diamino acid derivatives.



In summary, we have demonstrated, for the first time, the stereoselective amination of electron-deficient C(sp^3)−H bonds by applying Co(II)-based metalloradical catalysis to intramolecular α-C−H amination of esters, amides, ketones, and nitriles. In addition to high-yielding performance and its neutral and nonoxidative conditions, the Co(II)-catalyzed amination can proceed with high regio- and diastereoselectivity. Among other potential applications, the catalytic process offers an enabling approach for the stereoselective synthesis of α-amino acid derivatives through direct α-C−H amination of the corresponding esters and amides. We have shown, through the combination of a competition reaction, measurement of the kinetic isotope effect, and radical trapping experiment, that the unparalleled profile of activity and selectivity exhibited by Co(II)-catalyzed amination is attributed to its unique radical mechanism that involves the Co(III)-nitrene radical intermediate undergoing a stepwise radical abstraction−substitution pathway. As a further outcome of metalloradical catalysis, C−H bond-dissociation energy (BDE) is recognized as a fundamentally important factor in controlling and differentiating the reactivity and selectivity of various C−H bonds.

Acknowledgment. We are grateful for financial support by the NSF (CHE-1152767) and NIH (R01-GM098777).

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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The authors declare no competing financial interest.