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Regioselective Synthesis of Multisubstituted Furans via Metalloradical Cyclization of Alkynes with α -Diazocarbonyls: Construction of Functionalized α -Oligofurans

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Abstract

Co(III)-carbene radicals generated from activation of α -diazocarbonyls by Co(II) porphyrin complexes have been shown to undergo a new type of tandem radical addition reaction with alkynes to construct 5-membered furan structures. Cobalt(II) complex of 3,5-Di^tBu-IbuPhyrin, [Co(**P1**)], has proven to be effective in catalyzing the metalloradical cyclization reaction under neutral and mild conditions. The [Co(**P1**)]-catalyzed process is suitable to a wide range of α -diazocarbonyls and terminal alkynes with varied steric and electronic properties, producing polyfunctionalized furans with complete regioselectivity. The catalytic synthesis features a high degree of functional group tolerance and can be applied for construction of functionalized α -oligofurans through an iterative radical cyclization procedure.

Polyfunctionalized furans constitute an important class of five-membered *O*-heterocycles with widespread applications.¹ Their oligomers have also attracted considerable interest due to their great potential in material science.² Transition metalcatalyzed cyclization reactions, especially intermolecular cyclizations of structurally simple starting materials, are among the most direct and practical methods for the construction of substituted furans.³ Owing to synthetic ease of the substrates and mild reaction conditions, such transformations have received increasing attention and have been recognized as some of the most appealing directions in the synthesis of polyfunctionalized furans.^{3b–f, 3h–j} The Rh₂-catalyzed [3+2] cycloaddition of arylacetylenes with α -diazocarbonyl compounds represents one of the most direct approaches for the construction of polysubstituted furans.⁴ Electron-rich arylacetylenes have been shown to form furans with different acceptor/acceptor-substituted diazo reagents efficiently as they tend to stabilize the key zwitterionic intermediate.^{4b} Without the stabilization of the key intermediate provided by electron-rich arylacetylenes, other types of alkyne substrates, such as aliphatic and electron-deficient alkynes,^{4b,5} generally performed poorly in the Rh₂-based furan synthesis except in some specific cases where cyclic α -diazocarbonyls were employed⁶ or it was carried out in an intramolecular fashion.⁷ Moreover, direct access of furans with sensitive functionalities remains challenging in Rh₂- and other metal-based cycloaddition systems,^{3,4b,8} which share common reaction mechanisms that are intrinsically ionic in nature. Evidently, there is a need to develop new catalytic systems for general and effective syntheses of polyfunctionalized furans from different alkynes and α -diazocarbonyls. To meet the remaining challenges in the field, it seems desirable to establish a fundamentally different catalytic system that operates in a nonionic manner.

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

Structurally well-defined cobalt(II) complexes of porphyrins [Co(Por)] have emerged as unique metalloradical catalysts for olefin cyclopropanation.⁹ Mechanistic studies have confirmed that the Co(II)-based metalloradical cyclopropanation proceeds through an unusual Co(III)-carbene radical intermediate undergoing a stepwise radical addition-substitution pathway.¹⁰ Applying the metalloradical catalysis to alkyne substrates, a highly enantioselective cyclopropanation process has been recently developed (Scheme 1; Cycle I).¹¹ To further explore the application of metalloradical catalysis for other radical cyclization reactions, we envisioned the possibility of an alternative catalytic pathway that would lead to construction of 5-membered furan structures (Scheme 1; Cycle II). In this alternative process, the vinyl radical intermediate **B** generated from radical addition of Co(III)-carbene radical **A** to the alkyne would undergo a consecutive radical addition to the carbonyl group to give new intermediate **C**, which would release the furan product via radical β -scission. In addition to its fundamental importance, this catalytic tandem radical addition process would be synthetically attractive, as it would enable the direct synthesis of multisubstituted furans from α -diazocarbonyls and simple acetylenes. More importantly, owing to its nonionic mechanism, a general furan synthesis with a high degree of tolerance for functional groups would be achievable.

As a result of our efforts toward this proposed project, herein we report a general and regioselective synthesis of polyfunctionalized furans through intermolecular radical cyclization of acetylenes with acceptor/acceptor-substituted diazo reagents via Co(II)-based metalloradical catalysis. By way of an unprecedented tandem addition pathway of Co(III)-carbene radicals, this new catalytic system has a broad substrate scope and can be applied to various combinations of α -diazocarbonyls and terminal acetylenes, including challenging aliphatic and electron-deficient alkynes. Furthermore, the metalloradical cyclization process can tolerate various functionalities, such as -NR₂, -CHO, and -OH groups.

Initial efforts were focused on investigating the possibility of [Co(Por)]-catalyzed furan formation from the reaction of phenylacetylene with α -cyanodiazooacetate **2a** (Table 1), which was previously shown to undergo cyclopropanation.¹¹ Using the cobalt(II) complex of D_{2h}-symmetric amidoporphyrin 3,5-Di^tBu-IbuPhyrin, [Co(**P1**)], as the catalyst,¹² we observed a significant dependence of product distribution on reaction temperature. While the reaction at room temperature produced cyclopropene **4aa** predominantly, furan **3aa** was indeed detected as the minor product and isolated in 31% yield (entry 1). To our delight, when the reaction temperature was increased to 80 °C, 2,3,5-trisubstituted furan **3aa** was produced as the only regioisomer in 68% yield (entry 2). 2-Diazomalonates have been commonly used to prepare cyclopropene derivatives through Rh₂-catalyzed cyclopropanation of phenylacetylene.^{4b,13} Although a slow reaction was observed at room temperature, interestingly, 2-diazomalonate **2b** underwent effective [Co(**P1**)]-catalyzed cyclization with phenylacetylene at 80 °C to regioselectively form the 2,3,5-trisubstituted furan **3ab** in an excellent yield with almost no cyclopropanation product (entries 3 and 4).¹⁴ Further experiments showed that treatment of preprepared cyclopropene **4aa** or **4ab** in the presence of [Co(**P1**)], α -diazocarbonyl (**2a/b**) and acetylene **1a** at 80 °C resulted in ineffective isomerization to the corresponding furan **3**, indicating direct furan formation from cyclization of phenylacetylene with the diazo reagent rather than from ring expansion of the initially formed cyclopropene.¹⁵ These results clearly demonstrated that the Co(II)-catalyzed cyclopropanation pathway could be completely switched to furan formation through judicious use of the diazo reagent at a higher reaction temperature (Scheme 1).

The metalloradical catalyst [Co(**P1**)] was shown to be effective in catalyzing the cyclization of phenylacetylene with varied acceptor/acceptor-substituted diazo reagents at 80 °C, producing 2,3,5-trisubstituted furans with complete regioselectivity (Table 2). In addition to diazoacetates **2a** and **2b**, which formed the corresponding furans through cyclization with

the ester groups (entries 1 and 2), ketone groups could also effectively participate in the catalytic furan formation process as demonstrated with diazoketone **2c**, producing tosyl-substituted furan **3ac** in 87% yield (entry 3). More interestingly, α -ketodiaoacetates **2d** and **2e** could selectively cyclize with phenylacetylene to form furesters **3ad**^{15c} and **3ae**, respectively, indicating preferential involvement of ketone carbonyls over ester carbonyls in the [Co(**P1**)]-catalyzed furan synthesis (entries 4 and 5). Similar preference of aldehyde carbonyls over ester carbonyls was also observed for the metalloradical cyclization process. For example, when formyldiaoacetate **2f** was employed, 2,4-disubstituted furan **3af** was isolated as the sole furan product in 80% yield through a regioselective cyclization reaction of the aldehyde group (entry 6).

With the successful cyclization of phenylacetylene with varied diazo reagents for furan formation, the alkyne scope of the [Co(**P1**)]-catalyzed radical cyclization was then investigated in combination with different acceptor/acceptor-substituted diazo reagents.¹⁶ The Co(II)-based metalloradical system was found not only to be effective for acetylenes with different electronic properties, but also was able to tolerate many functional groups that would lead to side reactions in ionic processes (Table 3). For example, 4-(*N,N*-dimethylamino)phenylacetylene was fruitfully converted to 2,3,5-trisubstituted and 2,4-disubstituted furans through cyclization with different diazocarbonyls (entries 1–4, for single crystal structure of **3bh** see Supporting Information) without affecting the basic and electron-rich NMe₂ group. Arylacetylenes containing halogen and unprotected hydroxyl groups were also regioselectively cyclized by [Co(**P1**)] to form furans in good yields (entries 5 and 6). This noteworthy advantage of functional group tolerance with the Co(II)-based radical process is further demonstrated with reactions of substrates containing unprotected aldehyde groups. For example, cyclizations of 2-formylphenylacetylene with varied diazo reagents, including formyldiaoacetate **2f**, resulted in formation of aldehyde-containing furans in up to 96% yield (entries 7–10). Moreover, the Co(II)-catalyzed system could be extended for heteroaromatic and vinyl acetylenes, leading to high-yielding formation of corresponding 2,3,5-trisubstituted furans (entries 11–14).

In addition to conjugated acetylenes, the Co(II)-based metalloradical cyclization was shown to also be applicable to alkyl and silyl acetylenes (Table 3). For example, 1-octyne could be effectively cyclized with different acceptor/acceptor-substituted diazo reagents to form the corresponding furans in good yields (entries 15 and 16). Under similar conditions, trimethylsilylacetylene was successfully cyclized to produce furans bearing -TMS group (entries 17–19), which could potentially be deprotected to generate 2,3-substituted furans or replaced with other groups to form new furan derivatives. More significantly, ethynyl ester and ketone derivatives were shown to undergo the Co(II)-catalyzed furan cyclization in good to excellent yields (entries 20–22). This represents the first catalytic system that cyclizes electron-deficient alkynes with both cyclic and acyclic diazo reagents to form furan derivatives.

Through the use of appropriate diazo reagents, the Co(II)-based metalloradical cyclization could be carried out in tandem with two equivalents of alkynes, leading to a biscyclization process for construction of *O*-biheterocycles with interesting structures. For example, by employing 5-diazo-Meldrum's acid **2j**, a cyclic α -diaoacetate that has not been previously shown to cyclize with acetylenes to form heterocycles, two equivalents of arylacetylenes such as **1a** and **1l** could be successfully cyclized by [Co(**P1**)] to form bicyclic 6*H*-furo[2,3-*b*]pyran-6-one **5a** and **5l**, respectively (Scheme 2). The formation of *O*-biheterocycles **5** can be properly rationalized on the basis of the proposed general mechanism of metalloradical cyclization (Scheme 1; Cycle II). As detailed in Scheme 2, the tertiary radical intermediate **C**, generated from the initial sequence of consecutive radical addition (**A**→**B**→**C**), would undergo radical fragmentation via consecutive radical scission of two β -C–O bonds

(**C**→**D**→**E**) to give the key acyl radical intermediate **E**.¹⁷ The release of acetone, which was confirmed experimentally (see Supporting Information), presumably drives the radical β -scission of the two C–O bonds rather than the Co–C bond in **C**. Further radical addition-substitution of the acyl radical **E** with another molecule of alkyne would lead to formation of spiro compound **G**, which rearranged to a thermally more stable product **5**.¹⁸ The nature of 6*H*-furo[2,3-*b*]pyran-6-one **5a** was further established through X-ray structure analysis of its derivative furan-2(3*H*)-one **6a** (see Supporting Information), which was readily obtained from **5a** via hydrolysis and isomerization (Scheme 2).

Due to their great potential as a new class of organic electronic materials, oligofurans have attracted increasing interest.² While α -oligofurans have been recently prepared from presynthesized furan monomers through coupling reactions,^{2d} their direct synthesis from acyclic precursors, an approach that would be highly attractive, has remained largely underdeveloped. As an application of the Co(II)-based metalloradical cyclization, an effective process based on iterative radical cyclization was developed for construction of functionalized α -oligofurans with different numbers of furan units (Scheme 3). The key to its success is the design and synthesis of the bifunctional ketodiazooacetate **7** bearing a TMS-protected internal alkyne unit, which was effectively cyclized with phenylacetylene by [Co(**P1**)], affording furan monomer **F1** without affecting the internal triple bond. Monomer **F1** was readily desilylated with K₂CO₃ to provide **F1_H** whose terminal alkyne could be cyclized again with **7** to afford α -furan dimer **F2**. Reiteration of the desilylation and cyclization steps should lead to construction of functionalized α -oligofurans with specific number of repeating units and well-defined structures, as successfully demonstrated with the subsequent synthesis of α -furan trimer **F3** and tetramer **F4** (Scheme 3). The single crystal structure of **F3** clearly revealed a highly planar conformation in spite of the presence of the ester functionalities (Scheme 3; see Supporting Information). Initial studies showed that the solution of **F2-4** in THF, which were highly fluorescent, gave optical spectra with structured absorption bands of longer wavelength than **F1**. More interestingly, the absorption was further redshifted with growing number of furan units, indicating the increase in conjugation in **F2-4** (Figure 1).

In summary, we have developed a new catalytic system based on Co(II) metalloradical catalysis for regioselective furan synthesis from cyclization of alkynes with diazocarbonyls. This metalloradical cyclization enjoys a wide substrate scope with an exceptionally high degree of functional group tolerance, permitting effective access of multisubstituted furans with diverse functionalities. The Co(II)-catalyzed reaction has been successfully applied for the construction of *O*-biheterocycles and α -oligofurans, respectively, through double and iterative radical cyclization processes. The first demonstration of Co(II)-based metalloradical catalysis for five-membered heterocyclization involving tandem radical addition to C $\equiv$ C and C=O bonds may stimulate further development of new catalytic radical cyclization processes for selective syntheses of more diverse carbo- and heterocycles.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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References

1. (a) Hou, XL.; Yang, Z.; Wong, HNC. *Progress in Heterocyclic Chemistry*. Gribble, GW.; Gilchrist, TL., editors. Vol. 15. Pergamon; Oxford: 2003. p. 167(b) Keay, BA.; Dibble, PW. *Comprehensive Heterocyclic Chemistry II*. Katritzky, AR.; Rees, CW.; Scriven, EFV., editors. Vol. 2. Elsevier; Oxford: 1997. p. 395
2. (a) Gidron O, Shimon LJW, Leitun G, Bendikov M. *Org Lett*. 2012; 14:502. [PubMed: 22236351] (b) Gidron O, Dadvand A, Sheynin Y, Bendikov M, Perepichka DF. *Chem Commun*. 2011; 47:1976.(c) Bunz UHF. *Angew Chem, Int Ed*. 2010; 49:5037.(d) Gidron O, Diskin-Posner Y, Bendikov M. *J Am Chem Soc*. 2010; 132:2148. [PubMed: 20121137]
3. For recent reviews, see: Godoi B, Schumacher RF, Zeni G. *Chem Rev*. 2011; 111:2937. [PubMed: 21425870] Cadierno V, Crochet P. *Curr Org Synth*. 2008; 5:343. Patil NT, Yamamoto Y. *Arkivoc*. 2007:121.D'Souza DM, Muller TJJ. *Chem Soc Rev*. 2007; 36:1095. [PubMed: 17576477] Kirsch SF. *Org Biomol Chem*. 2006; 4:2076. [PubMed: 16729118] Brown RCD. *Angew Chem, Int Ed*. 2005; 44:850.Hou XL, Cheung HY, Hon TY, Kwan PL, Lo TH, Tong SY, Wong HNC. *Tetrahedron*. 1998; 54:1955.For selected recent examples on transition-metal-catalyzed intermolecular synthesis of furans, see: Lenden P, Entwistle DA, Willis MC. *Angew Chem, Int Ed*. 2011; 50:10657.Donohoe TJ, Bower JF. *Proc Natl Acad Sci U S A*. 2010; 107:3373. [PubMed: 20142508] Krische MJ. *Proc Natl Acad Sci U S A*. 2010; 107:3279. [PubMed: 20167802] Zhang M, Jiang HF, Neumann H, Beller M, Dixneuf PH. *Angew Chem, Int Ed*. 2009; 48:1681.
4. (a) Briones JF, Davies HML. *Tetrahedron*. 2011; 67:4313.(b) Davies HML, Romines KR. *Tetrahedron*. 1988; 44:3343.
5. Pang W, Zhu SF, Xin Y, Jiang HF, Zhu SZ. *Tetrahedron*. 2010; 66:1261.
6. (a) Zhang ZH, Han JW, Zhu SZ. *Tetrahedron*. 2011; 67:8496.(b) Lee YR, Suk JY. *Tetrahedron Lett*. 2000; 41:4795.(c) Pirrung MC, Blume F. *J Org Chem*. 1999; 64:3642. [PubMed: 11674492] (d) Pirrung MC, Zhang JC, Morehead AT. *Tetrahedron Lett*. 1994; 35:6229.(e) Muller P, Allenbach YF, Bernardinelli G. *Helv Chim Acta*. 2003; 86:3164.
7. For furan formation via metal-catalyzed intramolecular cyclization of alkynyl diazo reagents, see: Padwa A, Straub CS. *J Org Chem*. 2003; 68:227. [PubMed: 12530844] Padwa A, Straub CS. *Org Lett*. 2000; 2:2093. [PubMed: 10891238] Gettewert V, Krebs F, Maas G. *Eur J Org Chem*. 1999:1213.Padwa A, Kinder FR. *J Org Chem*. 1993; 58:21.Padwa A, Dean DC, Fairfax DJ, Xu SL. *J Org Chem*. 1993; 58:4646.Padwa A, Krumpe KE, Gareau Y, Chiacchio U. *J Org Chem*. 1991; 56:2523.Padwa A, Chiacchio U, Garreau Y, Kassir JM, Krumpe KE, Schoffstall AM. *J Org Chem*. 1990; 55:414.Kinder FR, Padwa A. *Tetrahedron Lett*. 1990; 31:6835.
8. (a) Li HY, Hsung RP. *Org Lett*. 2009; 11:4462. [PubMed: 19739617] (b) Zhou L, Ma J, Zhang Y, Wang J. *Tetrahedron Lett*. 2011; 52:5484.(c) Zhao LB, Guan ZH, Han Y, Xie YX, He S, Liang YM. *J Org Chem*. 2007; 72:10276. [PubMed: 18041850] (d) He C, Guo S, Ke J, Hao J, Xu H, Chen H, Lei A. *J Am Chem Soc*. 2012; 134:5766. [PubMed: 22428614] (e) Yan RL, Huang J, Luo J, Wen P, Huang GS, Liang YM. *Synlett*. 2010:1071.
9. For recent examples, see: Xu X, Lu HJ, Ruppel JV, Cui X, de Mesa SL, Wojtas L, Zhang XP. *J Am Chem Soc*. 2011; 133:15292. [PubMed: 21870825] Zhu SF, Xu X, Perman JA, Zhang XP. *J Am Chem Soc*. 2010; 132:12796. [PubMed: 20735129] Doyle MP. *Angew Chem, Int Ed*. 2009; 48:850.Zhu SF, Ruppel JV, Lu HJ, Wojtas L, Zhang XP. *J Am Chem Soc*. 2008; 130:5042. [PubMed: 18357991] Zhu S, Perman JA, Zhang XP. *Angew Chem Int Ed*. 2008; 47:8460.Chen Y, Ruppel JV, Zhang XP. *J Am Chem Soc*. 2007; 129:12074. [PubMed: 17877352]
10. (a) Lu HJ, Dzik WI, Xu X, Wojtas L, de Bruin B, Zhang XP. *J Am Chem Soc*. 2011; 133:8518. [PubMed: 21563829] (b) Dzik WI, Xu X, Zhang XP, Reek JNH, de Bruin B. *J Am Chem Soc*. 2010; 132:10891. [PubMed: 20681723]
11. Cui X, Xu X, Lu HJ, Zhu SF, Wojtas L, Zhang XP. *J Am Chem Soc*. 2011; 133:3304. [PubMed: 21332140]
12. Ruppel JV, Jones JE, Huff CA, Kamble RM, Chen Y, Zhang XP. *Org Lett*. 2008; 10:1995. [PubMed: 18422325]
13. (a) Chuprakov S, Rubin M, Gevorgyan V. *J Am Chem Soc*. 2005; 127:3714. [PubMed: 15771503] (b) Liao LA, Zhang F, Yan N, Golen JA, Fox JM. *Tetrahedron*. 2004; 60:1803.

14. Use of [Co(TPP)] as the catalyst resulted in much slower reactions under same conditions, giving the products in poor yields.
15. (a) Chen J, Ni SJ, Ma SM. Synlett. 2011:931.(b) Chen J, Ma SM. Chem Asian J. 2010; 5:2415. [PubMed: 20806315] (c) Ma SM, Zhang JL. J Am Chem Soc. 2003; 125:12386. [PubMed: 14531663] (d) Rubin M, Ryabchuk PG. Chem Heterocycl Compd. 2012; 48:126.
16. Under current catalytic conditons, internal alkynes were found to be ineffective substrates for both cyclopropanation and furan formation.
17. (a) Chatgililoglu C, Crich D, Komatsu M, Ryu I. Chem Rev. 1999; 99:1991. [PubMed: 11849018] (b) Ryu I, Sonoda N, Curran DP. Chem Rev. 1996; 96:177. [PubMed: 11848749]
18. Huet F, Lechevallier A, Conia JM. Chem Lett. 1981:1515.

Figure 1.
Optical Spectra of α -Oligofurans **F1-4** in THF.

Scheme 1.
Competitive Pathways for Co(II)-Based Metalloradical Cyclization of Alkynes with α -Diazocarbonyl Reagents: Cyclopropanation versus Furan Formation

Proposed Mechanism:

Scheme 2.

Direct Construction of 6*H*-Furo[2,3-*b*]pyran-6-one Structures from Metalloradical Biscyclization of Alkynes with 5-Diazo-Meldrum's Acid by [Co(P1)]

Scheme 3.
Construction of Functionalized α -Oligofurans via Iterative Metalloradical Cyclization of Diazo **7**^a

Table 1

Influence of Diazo Reagent and Temperature on Formation of Furans versus of Cyclopropenes via Metalloradical Cyclization with Phenylacetylene by [Co(P1)]^a

entry	diazo	temp(°C)	3: yield (%) ^b	4: yield (%) ^b
1		25	3aa : 31%	4aa : 69%
2	2a	80	3aa : 68%	4aa : 30%
3		25	3ab : 13%	4ab : trace
4	2b	80	3ab : 91%	4ab : trace

^a Carried out under N₂ with 1.0 equiv of diazo reagent and 2.0 equiv of phenylacetylene in one-time fashion without slow addition of diazo reagents.

^b Isolated yields.

Table 2

[Co(P1)]-Catalyzed Formation of Multisubstituted Furans from Cyclization of Phenylacetylene with Various Acceptor/Acceptor-Substituted Diazo Reagents^a

entry	diazo	furan	yield(%) ^b
1	 2a	 3aa	68
2	 2b	 3ab	91
3	 2c	 3ac	87
4	 2d	 3ad	73
5	 2e	 3ae	68
6	 2f	 3af	80

^a Carried out under N₂ with 1.0 equiv of diazo reagent and 2.0 equiv of phenylacetylene in one-time fashion without slow addition of diazo reagents.

^b Isolated yields.

Table 3

Synthesis of Multisubstituted Furans from Metalloradical Cyclization of Different Combinations of Alkynes and Diazo Reagents by [Co(P1)]^{a,b}

^a Carried out under N₂ with 1.0 equiv of diazo reagent and 2.0 equiv of acetylene in one-time fashion without slow addition of diazo reagents.

^b Isolated yields.

^c Structure determined by anomalous-dispersion effects in X-ray diffraction measurements on the crystal.

^d At 100 °C for 24 h.