J|A|C|S COMMUNICATIONS

Published on Web 08/25/2010

# A General and Efficient Cobalt(II)-Based Catalytic System for Highly Stereoselective Cyclopropanation of Alkenes with α-Cyanodiazoacetates

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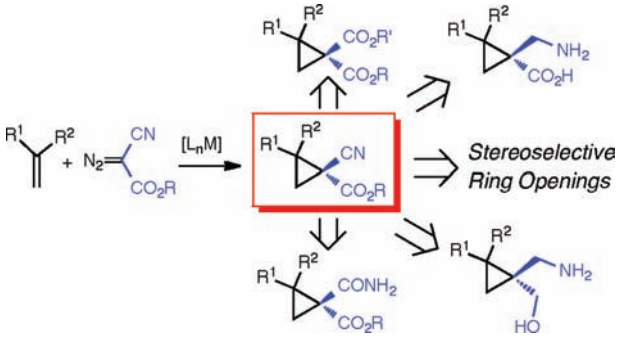
***Abstract:*** [Co(**P1**)], the cobalt(II) complex of the $D_2$-symmetric chiral porphyrin 3,5-Di$^t$Bu-ChenPhyrin, is an effective catalyst for catalyzing asymmetric olefin cyclopropanation with the acceptor/acceptor-type diazo reagent α-cyanodiazoacetates. The [Co(**P1**)]-catalyzed reaction is versatile and suitable for both aromatic and aliphatic olefins with varied electronic properties, including electron-rich and -poor olefins. The Co(II)-based catalytic system can be operated in a one-time protocol under mild conditions, affording the desired cyclopropane products in high yields with both high diastereo- and enantioselectivity. The resulting enantiomerically enriched 1,1-cyclopropanenitrile esters provide convenient access to a number of densely functionalized chiral cyclopropane derivatives, including α-cyclopropyl-$\beta$-amino acids.

Catalytic asymmetric cyclopropanation of alkenes with diazo reagents represents one of the most general and direct approaches for stereoselective synthesis of chiral cyclopropane derivatives, which have found widespread applications.[1] Considering the common existence of alkene units and the broad accessibility of diazo reagents with various combinations of α-groups, this thermodynamically favorable approach should, in principle, permit the construction of three-membered, all-carbon ring structures bearing all types of substituted functionalities. During the past two decades, a number of highly effective catalytic systems have been developed for various asymmetric cyclopropanation reactions with donor/acceptor- and acceptor-substituted diazo reagents.[2] The potential of catalytic asymmetric cyclopropanation, however, has not been fully extended to acceptor/acceptor-substituted diazo reagents owing to their low reactivity and poor stereocontrollability.[2−4]

***Scheme 1.*** Synthesis of 1,1-Cyclopropanenitrile Esters *via* Catalytic Asymmetric Cyclopropanation and Their Further Transformations




α-Cyanodiazoacetates (CDA) are a class of known acceptor/acceptor-substituted diazo reagents that have not been successfully employed for asymmetric olefin cyclopropanation.[5−8] This catalytic process would be highly desirable, as the resulting cyclopropanes bearing geminal nitrile and ester functionalities can be further transformed into a number of densely functionalized chiral cyclopropane molecules, including synthetically and biologically important cyclopropyl-amino acids and -amino alcohols (Scheme 1).[9] While the only study on the intramolecular version of the catalytic process gave results that are highly substrate-dependent (yield: 11−85%; ee: 29−91%),[8] it is strikingly noted that there has been no prior report on intermolecular asymmetric cyclopropanation with CDA. Moreover, the only intermolecular report of the catalytic process is nonasymmetric with poor diastereoselectivity (10−20% de), which highlights the challenges of stereocontrol for cyclopropanation with acceptor/acceptor-substituted diazo reagents.[7] It is evident that this important catalytic cyclopropanation process is largely undeveloped and that more reactive and stereodiscriminating catalysts are needed to address this unsolved problem in the field.

Structurally well-defined cobalt(II) complexes of $D_2$-symmetric chiral porphyrins [Co($D_2$-Por*)] have emerged as a new class of effective catalysts for asymmetric cyclopropanation.[3a,10] The Co(II)-based metalloradical cyclopropanation (MRC) has been shown to possess a different reactivity profile from the widely studied $Rh_2$- and Cu-based systems[3a,11] and can achieve highly stereoselective cyclopropanation of electron-deficient olefins[10f] and with acceptor/acceptor-substituted diazo reagents.[4d] In view of their unique catalytic activities, we decided to investigate the potential of [Co($D_2$-Por*)]-based catalysts for asymmetric cyclopropanation with α-cyano diazoacetates. As the outcome of this investigation, herein we wish to report the first catalytic system that is efficient for stereoselective cyclopropanation with α-cyano diazoacetates. In addition to high yields, the Co(II)-catalyzed reactions allow for excellent control of both diastereo- and enantioselectivity. Furthermore, the catalytic process has a broad substrate scope and can cyclopropanate both aromatic and aliphatic olefins having a wide range of electronic properties.

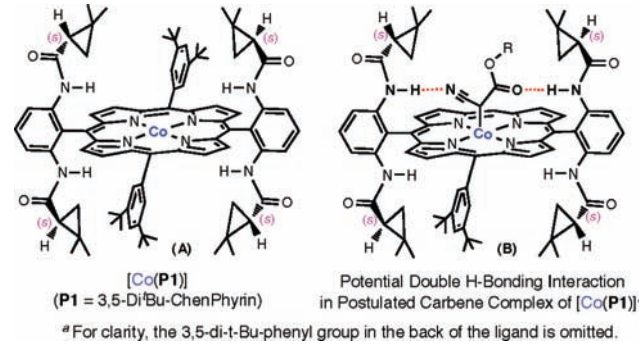



***Figure 1.*** Structures of $D_2$-symmetric chiral cobalt(II) porphyrins.

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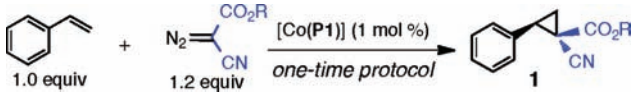
10.1021/ja1056246 

Regarding the family of [Co($D_2$-Por*)] with tunable electronic, steric, and chiral environments,[3a,10d,g] our previous study revealed that [Co(**P1**)], the cobalt(II) complex of the $D_2$-symmetric chiral porphyrin 3,5-Di$^t$Bu-ChenPhyrin (Figure 1A), is the optimal catalyst for asymmetric olefin cyclopropanation with α-nitrodiazoacetates (NDA).[4d] We rationalized the catalytic effectiveness of [Co(**P1**)] toward NDA as a consequence of two potential N−H---O hydrogen bonding interactions between two of the chiral cyclopropyl amide N−H elements on the **P1** ligand with both the N═O (−$NO_2$ group) and the C═O (−$CO_2$Et group) units of the carbene moiety, respectively, in a postulated metallocarbene intermediate.[4d] Given that a cyano group is normally considered a stronger hydrogen bond acceptor than a nitro group,[12] we envisioned a similar cobalt-carbene intermediate with the unique double-hydrogen bonding to be also potentially operative for CDA reactions (Figure 1B). On the basis of this hypothesis, initial efforts were made to systematically investigate asymmetric cyclopropanation reactions of styrene as a model substrate with CDA by [Co(**P1**)] under different conditions.

***Table 1.*** Asymmetric Cyclopropanation of Styrene with α-Cyano Diazoacetate by $D_2$-Symmetric Chiral Cobalt(II) Porphyrin [Co(**P1**)][a]




| entry | R | solvent | temp (°C) | yield (%)[b] | E:Z[c] | ee (%)[d] |
|---|---|---|---|---|---|---|
| 1 | Et | $CH_2Cl_2$ | 25 | 99 | 84:16 | 62 |
| 2 | Et | $C_6H_5Cl$ | 25 | 92 | 84:16 | 66 |
| 3 | Et | $C_2H_4Cl_2$ | 25 | 99 | 81:19 | 71 |
| 4 | Et | $C_6H_5Me$ | 25 | 94 | 85:15 | 70 |
| 5 | Et | $n$-$C_6H_{14}$ | 25 | 99 | 88:12 | 74 |
| 6 | $t$-Bu | $n$-$C_6H_{14}$ | 25 | 89 | >99:1 | 91 |
| 7 | $t$-Bu | $n$-$C_6H_{14}$ | 0 | 83 | >99:1 | 95 |
| 8 | $t$-Bu | $n$-$C_6H_{14}$ | −20 | 96 | >99:1 | 98 |

[a] Performed in one-time fashion for 24 h using 1 mol % [Co(**P1**)] under $N_2$ with 1.0 equiv of styrene and 1.2 equiv of α-cyano diazoacetates. [styrene] = 0.25 M. [b] Isolated yields. [c] Determined by NMR. [d] Enantiomeric excess of *E* major diastereomer determined by chiral HPLC.

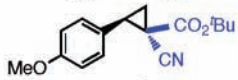
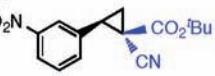
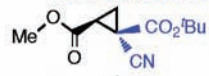
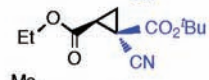
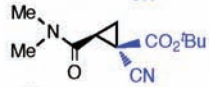
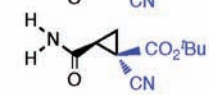
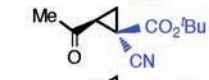
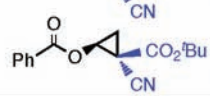
As summarized in Table 1, using the typical one-time protocol that has been enjoyed by Co(II)-based MRC,[10,11] styrene could be effectively cyclopropanated by 1 mol % of [Co(**P1**)] in dichloromethane with ethyl α-cyanodiazoacetate (ECDA) at room temperature, affording the desired product in almost quantitative yield with promising diastereo- and enantioselectivity (entry 1). To further improve the stereoselectivities, different solvents were evaluated. When the reaction was carried out in chlorobenzene, it increased the enantiomeric excess with no change in the diastereomeric ratio (entry 2). Further improvement in enantioselectivity was observed when dichloroethane was used as the solvent, but with a decreased diastereoselectivity (entry 3). To diverge from using chlorinated solvents, the reaction was then tested in toluene, resulting in improved diastereo- and enantioselective controls (entry 4). Subsequent experiments indicated *n*-hexane is the solvent of choice for the catalytic reaction. It provided the best enantiomeric excess and diastereomeric ratio while maintaining an excellent yield (entry 5). Under the same reaction conditions, use of *tert*-butyl α-cyanodiazoacetate (*t*-BCDA) instead of ECDA afforded the corresponding *E*-cyclopropane as the only diastereomer in 91% ee, albeit in a relatively lower yield (entry 6). The enantioselectivity was further enhanced to 95% ee without affecting the excellent diastereoselectivity when the reaction was executed at 0 °C (entry 7). A continued increase in enantiocontrol was observed when the reaction temperature was further lowered to −20 °C, achieving 98% ee and with the preservation of the complete *E*-diastereoselectivity (entry 8). To our delight, the reaction yield surprisingly rose back to 96%, presumably due to elimination of possible side reactions associated with *n*-hexane at this low temperature.

With the success of asymmetric cyclopropanation of styrene, the scope of the [Co(**P1**)]/*t*-BCDA-based catalytic system was then investigated in detail. As summarized in Table 2 (entries 1−5), styrene derivatives bearing substituents with varied electronic properties could also be successfully cyclopropanated under similar reaction conditions. For example, the cyclopropanation of styrene derivatives substituted with electron-donating MeO- as well as electron-withdrawing $CF_3$- and $NO_2$-groups productively generated the corresponding cyclopropanenitrile esters **1b**−**d** with essentially the same high stereoselectivities as the styrene product **1a**, even though in relatively lower yields (entries 1−4). Furthermore, even the extremely electron-poor pentafluorostyrene could be cyclopropanated by [Co(**P1**)], affording the desired product **1e** with essentially complete control of both diastereo- and enantioselectivity, albeit in a lower yield (entry 5). The absolute configuration of **1e** was established as [*1R,2S*] by anomalous-dispersion effects in X-ray diffraction measurements on the crystal (see the Supporting Information).

In addition to aromatic olefins, [Co(**P1**)] was also shown to be an effective catalyst for the cyclopropanation of electron-deficient olefins with CDA, another unique catalytic property of [Co(Por)]-based MRC that is absent in existing nonmetalloradical-based catalytic systems.[10,11] As presented in Table 2 (entries 6−11), various α,β-unsaturated carbonyl compounds and nitriles could be selectively cyclopropanated with *t*-BCDA by [Co(**P1**)], furnishing a series of densely functionalized cyclopropane structures. For instance, under modified reaction conditions (Table S1 in the Supporting Information), both methyl and ethyl acrylates could be catalytically converted to the desired cyclopropanenitrile diesters **1f** and **1g** in 90% and 79% yields, respectively, as single diastereomers with high enantiocontrol (entries 6 and 7). Both substituted and primary acrylamides were also suitable substrates for the catalytic system, providing the corresponding cyclopropane derivatives **1h** and **1i** bearing three different electron-withdrawing functionalities, including cyano, amido, and ester groups, in similar high yields and stereoselectivities (entries 8 and 9). It is notable that all the functional groups were well tolerated; potentially competitive N−H carbene insertion was not observed. Similarly, cyclopropane structures containing ketone, amido, and ester groups as three different ring substituents could be stereoselectively constructed from the reactions of acrylketones as demonstrated by the formation of **1j** (entry 10). Electron-deficient alkenes bearing cyano groups, such as acrylonitriles, could also be successfully cyclopropanated, as exemplified with the nearly quantitative formation of **1k**, albeit in lower stereoselectivities (entry 11).

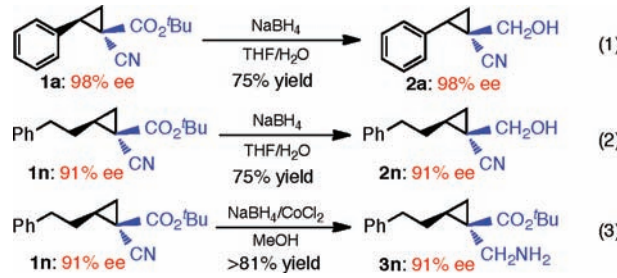
In addition to electron-deficient nonaromatic olefins, other nonaromatic olefins were also found to be suitable substrates for the [Co(**P1**)]/*t*-BCDA-based catalytic system. As displayed in Table 2 (entries 12−18), simple aliphatic olefins such as 1-hexene, 1-octene, and 4-phenyl-1-butene could be fruitfully converted to the desired products in high yields as single diastereomers with high enantioselectivities when the cyclopropanation reactions were conducted under solvent-free conditions (entries 12−14). Under similar conditions, electron-rich vinyl esters such as vinyl acetate, pivalate, and benzoate could also be productively cyclopropanated,

***Table 2.*** [Co(**P1**)]-Catalyzed Diastereo- and Enantioselective Cyclopropanation of Alkenes with *tert*-Butyl α-Cyanodiazoacetate[a]

| entry | cyclopropane | yield (%)[b] | E:Z[c] | ee (%)[d] | [α][e] |
|---|---|---|---|---|---|
| | *electron-rich and -poor aromatic olefins* | | | | |
| 1 |  **1a** | 96 | >99:1 | 98 | (–) |
| 2[g] |  **1b** | 88 | >99:1 | 99 | (–) |
| 3[g] |  **1c** | 81 | >99:1 | 98 | (–) |
| 4[g] |  **1d** | 90 | >99:1 | 98 | (–) |
| 5[h] |  **1e** | 73 | >99:1 | 99 | (–)[f] |
| | *electron-deficient nonaromatic olefins* | | | | |
| 6[i] |  **1f** | 90 | >99:1 | 88 | (–) |
| 7[i] |  **1g** | 79 | >99:1 | 92 | (–) |
| 8[j] |  **1h** | 99 | >99:1 | 87 | (–) |
| 9[k] |  **1i** | 72 | >99:1 | 82 | (–) |
| 10[j] |  **1j** | 81 | >99:1 | 92 | (–) |
| 11[j] |  **1k** | 99 | 72:28 | 82 | (–) |
| | *simple aliphatic and electron-rich olefins* | | | | |
| 12[l] |  **1l** | 86 | >99:1 | ≥96[n] | (–) |
| 13[l] |  **1m** | 72 | >99:1 | ≥92[n] | (–) |
| 14[l] |  **1n** | 90 | >99:1 | 91 | (–) |
| 16[m] |  **1o** | 97 | >99:1 | 71 | (+) |
| 17[l] |  **1p** | 86 | >99:1 | 82 | (+) |
| 18[l] |  **1q** | 80 | >99:1 | 88 | (–) |

[a] Performed in *n*-hexane at −20 °C for 24 h using 1 mol % [Co(**P1**)] under $N_2$ with 1.0 equiv of alkene and 1.2 equiv of *t*-BCDA. [alkene] = 0.25 M. [b] Isolated yields. [c] Determined by NMR. [d] ee of *E* isomer determined by chiral HPLC. [e] Sign of optical rotation. [f] [1*R*,2*S*] absolute configuration determined by anomalous-dispersion effects in X-ray diffraction measurements on the crystal and optical rotation. [g] 0 °C→RT. [h] 0 °C→RT; 5 mol %. [i] In $C_2H_4Cl_2$; alkene/*t*-BCDA = 5:1; 5 mol %. [j] In $C_2H_4Cl_2$; alkene/*t*-BCDA = 1:2.5; 5 mol %. [k] In $C_2H_4Cl_2$ at RT; alkene/*t*-BCDA = 1:2.5; 5 mol %. [l] No solvent; 48 h; 5 mol %. [m] At RT; no solvent; 48 h; 5 mol %. [n] ee of *E* isomer determined by chiral HPLC *via* derivatization.

offering the corresponding donor−acceptor cyclopropanes in high yields as sole diastereomers, albeit in relatively low enantiomeric excesses (entries 16−18).




With a viable route to these highly functionalized cyclopropyl nitrile esters in enantioenriched forms by [Co(**P1**)]-catalyzed cyclopropanation, we are currently working on exploring their potential applications as chiral building blocks for various stereoselective syntheses (Scheme 1). As an initial part of this exploration, the ester groups in both **1a** and **1n** could be selectively reduced to the corresponding primary alcohols **2a** and **2n** with full retention of the configuration (eqs 1 and 2).[9d] Alternatively, the cyano group in **1n** was discriminately converted to a primary amine without affecting the ester functionality under different reduction conditions (eq 3).[9d] Again, the stereochemistry was completely preserved.

In summary, we have demonstrated that [Co(**P1**)] is a versatile and efficient catalyst for highly diastereo- and enantioselective cyclopropanation of a broad range of different alkenes with α-cyanodiazoacetates.[13] The Co(II)-based system represents the first successful example of using this class of acceptor/acceptor-substituted diazo reagents for the asymmetric cyclopropanation process. The resulting chiral nonracemic cyclopropane derivatives bearing densely functionalized groups possess a myriad of potential synthetic and biological applications (Scheme 1). More broadly, the establishment of α-cyanodiazoacetates as effective and selective carbene sources for cyclopropanation, taken together with other recent successes in the area,[4] may encourage further development of new catalytic systems for the wide use of this and other acceptor/acceptor-substituted diazo reagents for various stereoselective carbene transfer processes.

**Acknowledgment.** We are grateful for financial support by the National Science Foundation (CAREER Award: CHE-0711024).

**Supporting Information Available:** Experimental procedures, analytical data for all compounds, and complete ref 9d. This material is available free of charge via the Internet at http://pubs.acs.org.

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(11) In addition to the wide substrate scope and high selectivity (both diastereo- and enantioselectivity), the Co(II)-based MRC (metalloradical cyclopropanation) catalytic system enjoys a practical attribute that is atypical for metal-catalyzed carbene transfers: it can be operated in a one-time fashion with alkenes as limiting reagents and requires no slow addition of diazo reagents. For a mechanistic study on Co(II) porphyrin-catalyzed cyclopropanation, see: Dzik, W. I.; Xu, X.; Zhang, X. P.; Reek, J. N. H.; de Bruin, B. *J. Am. Chem. Soc.* **2010**, *132*, 10891.
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(13) Preliminary results showed some activated internal olefins can also be applied for the [Co(P1)]/*t*-BCDA-based catalytic system. For example, norbornene could be cyclopropanated to afford the desired product in 66% yield in favor of exo-isomer (exo:endo = 83:17). See Supporting Information for its X-ray structural determination and other characterization data. When indene was used as the substrate, the reactions gave low yields (10−20%). The asymmetric cyclopropanation of α-methylstyrene provided the desired cyclopropane product in 67% yield, 92% de, and 70% ee.

JA1056246