Asymmetric Cyclopropanation

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Acceptor/Acceptor-Substituted Diazo Reagents for Carbene Transfers: Cobalt-Catalyzed Asymmetric *Z*-Cyclopropanation of Alkenes with α-Nitrodiazoacetates**

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Cyclopropanes are an important class of compounds that have numerous fundamental and practical applications.[1] One of the most general approaches for the stereoselective construction of cyclopropanes, which are the smallest all-carbon cyclic molecules, is the metal-catalyzed asymmetric cyclopropanation of alkenes with diazo reagents.[2] Among the three classes of common diazo reagents,[3] acceptor-substituted diazo reagents, such as diazoesters, are well established as the most effective carbene sources for metal-catalyzed stereoselective cyclopropanation.[4] There has been great progress in metal-catalyzed selective carbene transfers with donor/acceptor-substituted diazo reagents such as vinyldiazoesters and aryldiazoesters.[3,5] However, asymmetric cyclopropanation with acceptor/acceptor-substituted diazo reagents remains a major challenge in the field because of their inherent low reactivity and perceived poor enantioselectivity.[2,3] Therefore, more reactive and enantiodiscriminating catalysts need to be developed to meet this challenge.[2,3]

A family of cobalt(II) D_2-symmetric chiral porphyrins [Co(Por)] with tunable electronic, steric, and chiral environments (Figure 1), has emerged as a new class of effective catalysts for various asymmetric cyclopropanation reactions, including that of electron-deficient olefins with diazosulfones.[6,7] Having recognized their distinct catalytic properties,[6–8] we initiated a project to examine the potential of Co^{II}-based catalysts for asymmetric cyclopropanation with acceptor/acceptor-substituted diazo reagents. Our first target was α-nitrodiazoacetates (NDAs),[9] as the resulting cyclopropanes have been demonstrated to be valuable precursors for a number of useful compounds, including the synthetically and biologically important cyclopropane α-amino acids and aminocyclopropanes (Scheme 1).[10] Among several previous efforts towards metal-catalyzed cyclopropanation with NDA,[10–13] it is notable that Charette et al. conducted a systematic evaluation of the reaction by employing various Rh- and Cu-based chiral catalysts.[12] While the desired cyclopropanes were obtained predominantly as *E* isomers in good yields, the best enantioselectivity, which was achieved by using a Cu-based catalyst in the presence of ethyl diazoacetate (20%) as additive, was 72% *ee*.[12,14] We report herein a Co^{II}-based catalytic system for highly

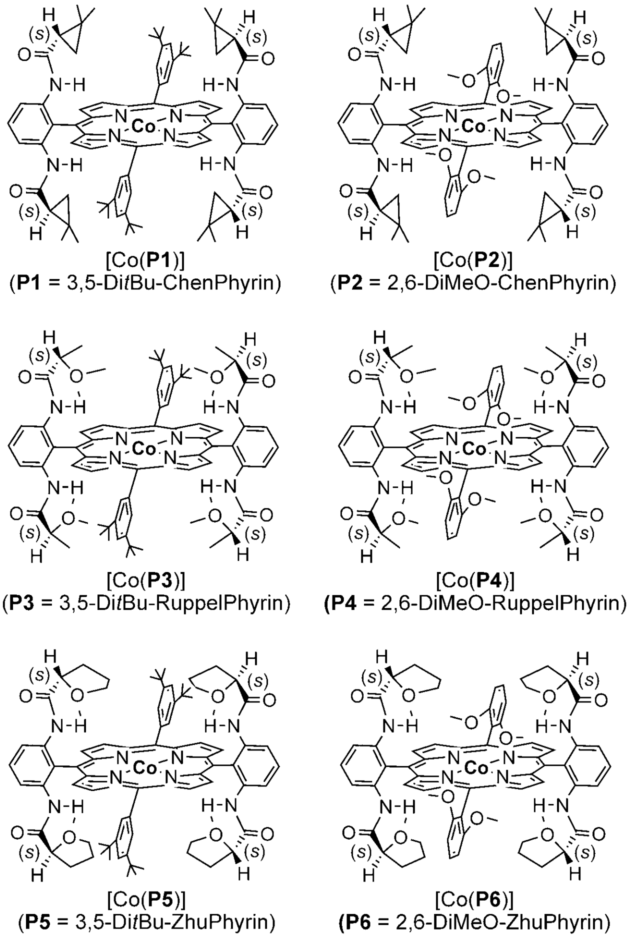
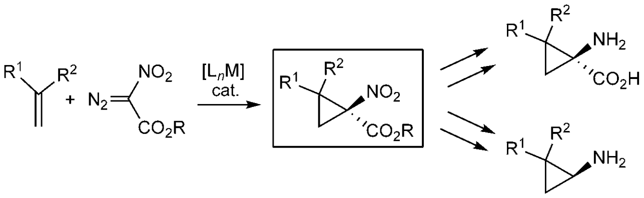

[Co(**P1**)] (**P1** = 3,5-Di*t*Bu-ChenPhyrin)
[Co(**P2**)] (**P2** = 2,6-DiMeO-ChenPhyrin)
[Co(**P3**)] (**P3** = 3,5-Di*t*Bu-RuppelPhyrin)
[Co(**P4**)] (**P4** = 2,6-DiMeO-RuppelPhyrin)
[Co(**P5**)] (**P5** = 3,5-Di*t*Bu-ZhuPhyrin)
[Co(**P6**)] (**P6** = 2,6-DiMeO-ZhuPhyrin)

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



Scheme 1. Synthesis and further reactions of cyclopropane nitroesters.

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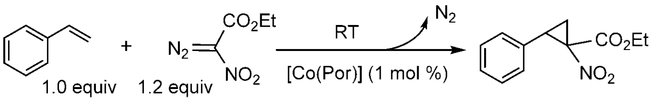
diastereo- and enantioselective cyclopropanation of various alkenes with NDA.[15] Furthermore, the catalytic process produced the atypical *Z* isomers as the dominant products.

Initial efforts were focused on the systematic evaluation of various catalytic conditions for the cyclopropanation of styrene with ethyl α-nitrodiazoacetates (ENDAs) by different [Co(Por)] (Table 1 and Table S1 in the Supporting Information). While the ineffectiveness of [Co(tpp)] (tpp = tetraphenylporphyrin) for the reaction might be expected (Table 1, entry 1), it was a disappointing revelation that [Co(**P6**)], which was previously shown to be the best catalyst for asymmetric cyclopropanation with diazosulfones,[6e] gave an even poorer result (Table 1, entry 7). However, in contrast to previous systems,[10–14] it was noted that the *Z*-cyclopropane was the major product. Subsequent experiments with other D_2-symmetric chiral porphyrins with varied environments revealed a dramatic ligand effect (Table 1, entries 2–7). Among them, [Co(**P1**)] proved to be the optimal catalyst, producing the *Z*-dominant cyclopropane α-nitroester ($Z/E = 91{:}09$) in 99% yield and 81% *ee* (Table 1, entry 2). The [Co(**P1**)]-based catalytic system was further improved by optimizing other reaction conditions (Table 1, entries 8–12 and Table S1 in the Supporting Information).

Table 1: Asymmetric *Z*-cyclopropanation of styrene with ethyl α-nitrodiazoacetate by D_2-symmetric chiral cobalt(II) porphyrins.[a]

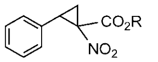
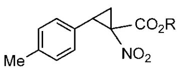
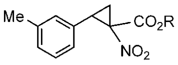
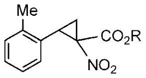
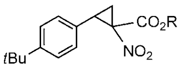
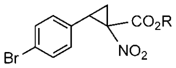
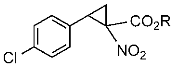
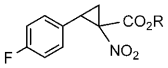
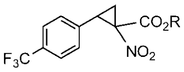
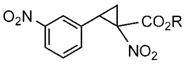
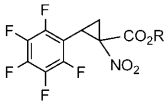
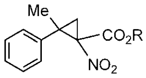
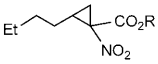
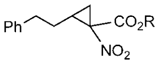
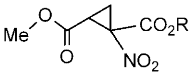
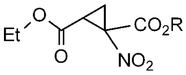
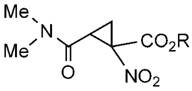


Entry	[Co(Por)][b]	Solvent	Yield [%][c]	Z/E[d]	ee [%][e]
1	[Co(tpp)]	CH_2Cl_2	15[f]	58:42	–
2	[Co(**P1**)]	CH_2Cl_2	99	91:09	81
3	[Co(**P2**)]	CH_2Cl_2	99	91:09	58
4	[Co(**P3**)]	CH_2Cl_2	20	67:33	33
5	[Co(**P4**)]	CH_2Cl_2	69	81:19	47
6	[Co(**P5**)]	CH_2Cl_2	31	66:34	−23
7	[Co(**P6**)]	CH_2Cl_2	< 5[f]	85:15	n.d.[g]
8	[Co(**P1**)]	$C_2H_4Cl_2$	91	93:07	86
9[h]	[Co(**P1**)]	$C_2H_4Cl_2$	90	92:08	90
10[i]	[Co(**P1**)]	$C_2H_4Cl_2$	98	92:08	92
11	[Co(**P1**)]	C_6H_5Cl	99	88:12	82
12	[Co(**P1**)]	n-C_6H_{14}	87	92:08	89

[a] Performed at RT for 24 h using 1 mol% [Co(Por)] under N_2 with 1.0 equiv of styrene (0.25 M) and 1.2 equiv of ENDA. [b] See Figure 1 for structures. [c] Isolated yields. [d] Determined by NMR. [e] *ee* of *Z* isomer determined by HPLC using a chiral stationary phase. [f] Estimated by NMR. [g] Not determined. [h] 0 °C; 2 mol% [Co(Por)]. [i] −20 °C; 5 mol% [Co(Por)].

The effectiveness of [Co(**P1**)] could perhaps be rationalized as a consequence of two potential N−H⋯O hydrogen-bonding interactions between two of the chiral amide N-H moieties on the **P1** ligand with both the N=O (-NO_2 group) and the C=O (-CO_2Et group) units of the carbene moiety, respectively. These interactions occur in a postulated metallocarbene intermediate[16] and would promote the carbene formation from the less reactive diazo reagent and rigidify the intermediate towards its subsequent reaction with the olefin substrate, which would lead to an more effective and selective catalytic process. While similar interactions would also exist in the [Co(**P2**)]-catalyzed reaction, the intercomponent

Table 2: [Co(**P1**)]-catalyzed diastereo- and enantioselective cyclopropanation of different alkenes with α-nitrodiazoacetates.[a]

Entry	Cyclopropane	R	Yield [%][b]	Z/E[c]	ee [%][d]	[α][e]
1		Et	87	92:08	89	(−)
2[g,h]		Et	93	92:08	92	(−)
3		tBu	91	> 99:1	91	(−)
4[g,h]		tBu	97	> 99:1	94	(−)
5[g,h]		Et	86[k]	93:07	90	(−)
6[h]		tBu	90	> 99:1	92	(−)
7[g,h]		Et	91	96:04	91	(−)
8[g,h]		Et	82	92:08	91	(−)
9[g,h]		Et	83	92:08	90	(−)
10[h]		tBu	87	> 99:1	92	(−)
11[g,h]		Et	84	91:09	90	(−)
12[g,h]		Et	82	91:09	90	(−)
13[g,h]		Et	87	91:09	90	(−)
14[g,h]		Et	88	92:08	90	(−)
15[h]		tBu	98	96:04	88	(−)
16		Et	90	91:09	94	(−)[f]
17[g,h]		Et	81	93:07	95	(−)[f]
18[h,l]		Et	51	90:10	82	(−)
19		Et	70[k]	94:06	83	(−)
20[h,m]		tBu	45	92:08	≥ 80[n]	(−)
21[h,m]		tBu	43	92:08	≥ 86[n]	(+)
22[h,j]		Et	42	53:47	88	(−)
23[h,j]		Et	62	56:44	88	(−)
24[h,j]		Et	92	63:37	75	(−)

[a] Performed in n-hexane at RT for 24 h under N_2 using [Co(**P1**)] 1 mol% with 1.0 equiv of alkene 0.25 M and 1.2 equiv of NDA. [b] Isolated yields. [c] Determined by NMR. [d] *ee* of *Z* isomer determined by HPLC using a chiral stationary phase. [e] Sign of optical rotation. [f] [1*S*,2*S*] absolute configuration determined by X-ray crystal structural analysis and optical rotation. [g] 0 °C → RT. [h] 5 mol%. [j] In $C_2H_4Cl_2$. [k] Determined by NMR. [l] Alkene/NDA = 5:1; 48 h. [m] No solvent; 48 h. [n] *ee* of *Z* isomer determined by chiral HPLC after derivatization.

hydrogen bonds between amides and carbene moieties in the cases of [Co(**P3**)]–[Co(**P6**)] would be inhibited or largely reduced as a result of the competitive N−H···O hydrogen-bonding interactions within the chiral amide units of the ligands (Figure 1).[6e]

Based on the optimized reaction conditions (Table 1), the substrate scope of the [Co(**P1**)]-based catalytic system was then examined. It was shown that the catalytic process could be successfully applied to different alkene substrates with various NDA derivatives (Table 2 and Table S2 in the Supporting Information). For example, in addition to styrene, various styrene derivatives containing groups at different ring positions could be effectively cyclopropanated with ENDA or *tert*-butyl α-nitrodiazoacetates (*t*BNDAs; Table 2, entries 1–17). As one of unique catalytic properties associated with the [Co(Por)]-based system,[6c] even the extremely electron-deficient pentafluorostyrene could be used as a substrate, albeit resulting in a somewhat lower yield (Table 2, entry 18). The use of α-methylstyrene allowed the stereoselective construction of a cyclopropane structure containing two contiguous quaternary stereogenic centers (Table 2, entry 19). When the cyclopropanation reaction was conducted under solvent-free conditions, aliphatic alkenes, which are typically challenging substrates for this reaction, were also successfully converted into the desired cyclopropanes with good diastereo- and enantioselectivity although in moderate yields (Table 2, entries 20–21). When 1,2-dichloroethane was used as solvent, electron-deficient olefins such as α,β-unsaturated esters and amides, which represent another series of challenging substrates,[6d] could be cyclopropanated as well, but with diminished diastereoselectivity (Table 2, entries 22–24). In most cases, however, the corresponding cyclopropane α-nitroesters were obtained predominantly as *Z* isomers in high yields with high enantioselectivities (Table 2 and Table S2 in the Supporting Information).

In summary, we have developed a general and highly asymmetric *Z*-cyclopropanation process with α-nitrodiazoacetates catalyzed by [Co(**P1**)]. This represents the first highly effective and selective catalytic system for asymmetric cyclopropanation with acceptor/acceptor-substituted diazo reagents as the carbene source. In addition to the well-documented synthetic utility of the resulting cyclopropane α-nitroesters,[8] the demonstration of α-nitrodiazoacetates as effective and selective carbene sources for cyclopropanation may stimulate further studies that will lead to the general use of acceptor/acceptor-substituted diazo reagents for catalytic carbene transfers.

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[8] In addition to the wide substrate scope and high selectivity (both diastereo- and enantioselectivity), the Co^{II}-based catalytic system enjoys a practical attribute that is atypical for metal-catalyzed carbene transfers—it can be operated in a one-pot fashion with alkenes as limiting reagents and requires no slow addition of diazo reagents.

[9] As reported in Ref. [11], α-nitrodiazoacetates were synthesized on multigram scales and were found to be stable for long storage periods without observation of decomposition or experience of explosion. In general, however, diazo reagents may be explosive and should be handled with great care.

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