

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 vinyl diazoesters and aryl diazoesters.^[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

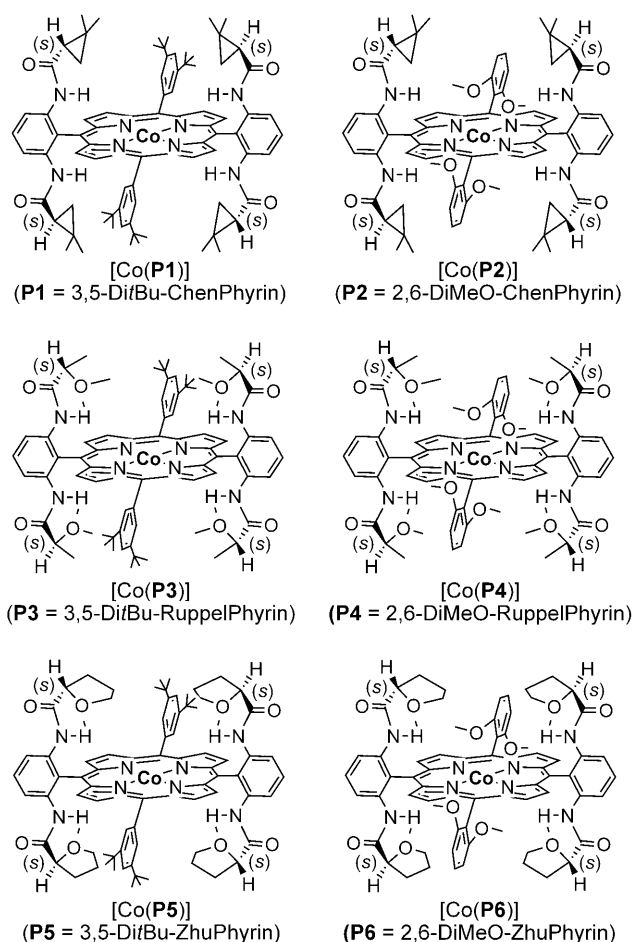
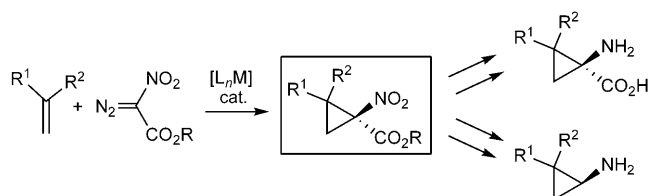


Figure 1. Structures of D_2 -symmetric chiral cobalt(II) porphyrins.



Scheme 1. Synthesis and further reactions of cyclopropane nitroesters.

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

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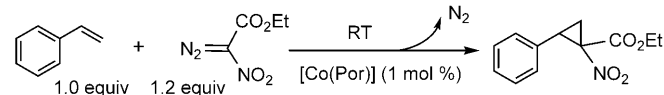
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diastereo- and enantioselective cyclopropanation of various alkenes with NDA.^[15] Furthermore, the catalytic process produced the atypical *Z* isomers as the dominant products.

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 Informa-

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]	<i>Z</i> / <i>E</i> ^[d]	<i>ee</i> [%] ^[e]
1	[Co(tpp)]	CH ₂ Cl ₂	15 ^[f]	58:42	—
2	[Co(P1)]	CH ₂ Cl ₂	99	91:09	81
3	[Co(P2)]	CH ₂ Cl ₂	99	91:09	58
4	[Co(P3)]	CH ₂ Cl ₂	20	67:33	33
5	[Co(P4)]	CH ₂ Cl ₂	69	81:19	47
6	[Co(P5)]	CH ₂ Cl ₂	31	66:34	—23
7	[Co(P6)]	CH ₂ Cl ₂	< 5 ^[f]	85:15	n.d. ^[g]
8	[Co(P1)]	C ₂ H ₄ Cl ₂	91	93:07	86
9 ^[h]	[Co(P1)]	C ₂ H ₄ Cl ₂	90	92:08	90
10 ^[i]	[Co(P1)]	C ₂ H ₄ Cl ₂	98	92:08	92
11	[Co(P1)]	C ₆ H ₅ Cl	99	88:12	82
12	[Co(P1)]	<i>n</i> -C ₆ H ₁₄	87	92:08	89

[a] Performed at RT for 24 h using 1 mol % [Co(Por)] under N₂ 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)].

tion). 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,^[6c] 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).

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 (–NO₂ group) and the C=O (–CO₂Et group) units of the carbene moiety, respectively. These interactions occur in a postulated metal-carbene 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

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

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

[a] Performed in *n*-hexane at RT for 24 h under N₂ 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 %. [i] In C₂H₄Cl₂. [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.

substrate, which would lead to a more effective and selective catalytic process. While similar interactions would also exist in the [Co(P2)]-catalyzed reaction, the intercomponent

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).^[6c]

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 (tBNDA; 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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