

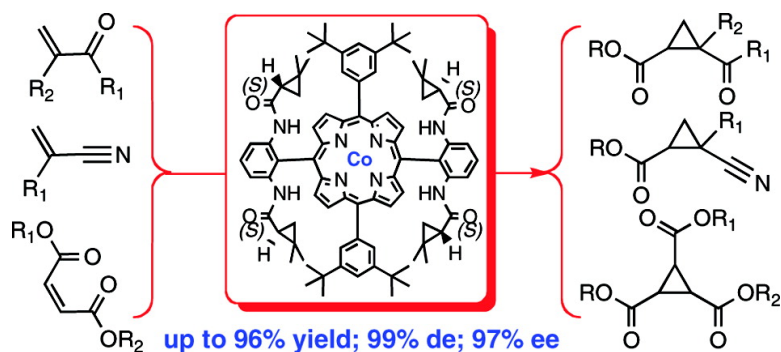
Communication

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*J. Am. Chem. Soc.*, **2007**, 129 (40), 12074-12075 • DOI: 10.1021/ja074613o • Publication Date (Web): 18 September 2007

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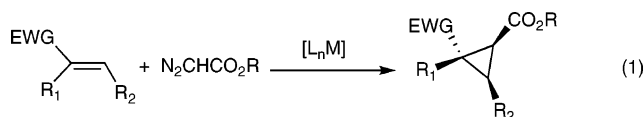
## Cobalt-Catalyzed Asymmetric Cyclopropanation of Electron-Deficient Olefins

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Metal-catalyzed cyclopropanation of olefins with diazo reagents has attracted great research interest because of its fundamental and practical importance.<sup>1</sup> The resulting cyclopropyl units are recurrent motifs in biologically important molecules and serve as versatile precursors in organic synthesis.<sup>1,2</sup> In the past two decades, outstanding asymmetric catalytic processes,<sup>1,2</sup> notably those based on copper,<sup>3</sup> rhodium,<sup>4</sup> and ruthenium,<sup>5</sup> have been developed to allow for the synthesis of chiral cyclopropane derivatives from olefins with diazoacetates in high yields and high selectivities. While a number of catalytic systems worked exceptionally well with styrene derivatives and some electron-rich olefins, asymmetric cyclopropanation of electron-deficient olefins containing electron-withdrawing groups (eq 1) such as  $\alpha,\beta$ -unsaturated carbonyl compounds and nitriles have proven to be a challenging problem presumably due to the electrophilic nature of the metal-carbene intermediates in the catalytic cycles.<sup>1,2</sup> This catalytic asymmetric process would be highly desirable as the corresponding electrophilic cyclopropanes containing two or more electron-withdrawing groups have shown to be valuable synthetic intermediates for various applications.<sup>6</sup>



Among several previous efforts toward metal-catalyzed cyclopropanation of electron-deficient olefins with diazo reagents,<sup>7–12</sup> the most notable example is the (Salen)Ru-based asymmetric catalytic system recently reported by Nguyen and co-workers.<sup>9</sup> It was shown that methyl methacrylate could be effectively cyclopropanated with ethyl diazoacetate (EDA) using a 5:1 ratio of olefin/EDA, producing the desired product in high yield and high selectivities (both diastereoselectivity and enantioselectivity).<sup>9</sup> However, only moderate results were obtained with acrylonitrile even when the reactions were run in neat olefin.<sup>9</sup> In this Communication, we wish to report a general and efficient catalytic system for asymmetric cyclopropanation of electron-deficient olefins. Building on our previous work on Co-based asymmetric cyclopropanation,<sup>13</sup> the Co(II) complex of the  $D_2$ -symmetric chiral porphyrin [Co(1)] (Figure 1) was found to cyclopropanate a wide range of  $\alpha,\beta$ -unsaturated carbonyl compounds and nitriles (eq 1), forming the corresponding electrophilic cyclopropane derivatives in high yields and selectivities. Furthermore, the [Co(1)]-based catalytic process could be operated efficiently at room temperature in a one-pot fashion with olefins as limiting reagents and would not require the slow addition of diazo reagents.

Our previous study on asymmetric cyclopropanation of styrene derivatives revealed that the [Co(1)]-based system seemed insensitive to substrate electronics.<sup>13</sup> Even the extremely electron-deficient pentafluorostyrene could be cyclopropanated.<sup>13c</sup> This result prompted us to evaluate the catalytic reactivity of [Co(1)] toward more challenging substrates such as electron-deficient non-styrene olefins (Table 1). Under the one-pot protocol where olefins are the limiting

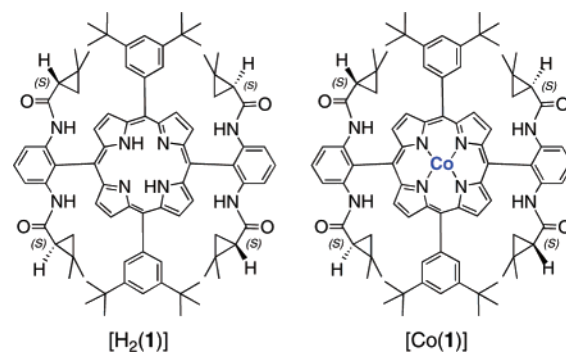


Figure 1. The  $D_2$ -symmetric chiral porphyrin and Co(II) complex.

reagent, using 1 mol % of [Co(1)] in the presence of 0.5 equiv of DMAP could effectively cyclopropanate both acrylates and methacrylates with EDA or *tert*-butyl diazoacetate (*t*-BDA) at room temperature in toluene, forming the corresponding 1,2-cyclopropanediester in good yields and high diastereo- as well as enantioselectivities (entries 1–5). Under the same conditions, acrylamide as well as its mono- and disubstituted derivatives were also suitable substrates, providing the corresponding 1,2-cyclopropaneamidoesters with good to high yields and excellent selectivities (entries 6–10). The amido functional groups were well-tolerated; no N–H insertion products were observed. Alkenes bearing carbonyl and cyano groups such as acrylketones and acrylonitriles were fully compatible with the catalytic system, as well. In most of the cases, the resulting 1,2-cyclopropaneketoesters (entries 11–15) and 1,2-cyclopropane cyanoesters (entries 16–19) could be synthesized in high yields and high selectivities. As the best example, cyclopropanation of 1-octen-3-one with *t*-BDA resulted in the formation of the desired *trans*-1,2-cyclopropaneketoester in 94% yield, 98% de, and 96% ee (entry 14). Diethyl maleate could also be successfully cyclopropanated to produce the 1,2,3-cyclopropanetriester solely as the  $\alpha,\alpha,\beta$ -isomer, albeit in a lower yield (entry 20).

While most of the substrates gave high yields and selectivities, the yields of several reactions were still moderate (Table 1). To further improve the catalytic process without sacrificing its attractive practicality, several common solvents in addition to toluene were evaluated for the cyclopropanation of ethyl acrylate with *t*-BDA under the same conditions. Among the solvents tested (Table 2), chlorobenzene was found to be the best solvent, giving the desired cyclopropane in the highest yield and with the best enantioselectivity as well as diastereoselectivity. As a result, several lower-yielding reactions were repeated in chlorobenzene. Dramatic improvements in yield were obtained while maintaining high diastereo- and enantioselectivities (Table 1, entries 1A–3A, 5A–7A, 10A, 15A, 18A, and 20A).

In summary, we have demonstrated that [Co(1)] is an effective catalyst for asymmetric cyclopropanation of various electron-deficient olefins under mild conditions, forming synthetically valuable electrophilic cyclopropane derivatives in high yields and high stereoselectivities. Together with its high reactivity and

**Table 1.** Diastereoselective and Enantioselective Cyclopropanation of Electron-Deficient Olefins Catalyzed by [Co(I)]<sup>a</sup>

entry	alkene	diazo	product	yield (%) <sup>b</sup>	tc <sup>d</sup>	ee (%) <sup>e</sup>
1		EDA		78	98:02	80 <sup>g</sup>
1A <sup>b</sup>				95	97:03	81 <sup>g</sup>
2		<i>t</i> -BDA		72	99:01	90
2A <sup>b</sup>				92	99:01	91
3		<i>t</i> -BDA		62	98:02	84
3A <sup>b</sup>				88	97:03	80
4		EDA		73	95:05	61
5		<i>t</i> -BDA		62	93:07	84
5A <sup>b</sup>				90	93:07	83
6		EDA		51	99:01	88
6A <sup>b</sup>				81	99:01	90
7		<i>t</i> -BDA		66	99:01	97
7A <sup>b</sup>				77	99:01	97
8		EDA		85	99:01	77
9		<i>t</i> -BDA		86	99:01	96
10		<i>t</i> -BDA		44	99:01	97
10A <sup>b</sup>				96	99:01	96
11		EDA		89	96:04	80
12		<i>t</i> -BDA		81	99:01	94
13		EDA		92	98:02	79
14		<i>t</i> -BDA		94	99:01	96
15		<i>t</i> -BDA		40	98:02	90
15A <sup>b</sup>				84	97:03	87
16		EDA		83	72:28	73
17		<i>t</i> -BDA		83	76:24	93
18		EDA		77	69:31	84
18A <sup>b</sup>				93	69:31	81
19		<i>t</i> -BDA		87	62:38	95
20		EDA		37	>99:1 <sup>f</sup>	--
20A <sup>b</sup>				94	>99:1 <sup>f</sup>	--

<sup>a</sup> Performed in toluene at rt for 20 h using 1 mol % of [Co(I)] under N<sub>2</sub> with 1.0 equiv of alkene and 1.2 equiv of EDA or *t*-BDA in the presence of 0.5 equiv of DMAP; [alkene] = 0.25 M. <sup>b</sup> Performed in chlorobenzene. <sup>c</sup> Isolated yields. <sup>d</sup> Determined by GC. <sup>e</sup> Determined by GC or HPLC on chiral stationary phases. <sup>f</sup> Only the  $\alpha,\alpha,\beta$ -isomer was observed. <sup>g</sup> A (-)-[1*R*,2*R*] absolute configuration was determined by optical rotation.

selectivity toward styrene derivatives shown previously,<sup>13</sup> [Co(I)] may be considered one of the most selective catalysts for asymmetric cyclopropanation of both electron-sufficient and electron-deficient olefins with diazoacetates.<sup>1-5</sup> These results suggest that the catalytic intermediate of the current Co(II)-based system may

**Table 2.** Solvent Effect in [Co(I)]-Catalyzed Diastereoselective and Enantioselective Cyclopropanation of Electron-Deficient Olefins<sup>a</sup>

entry	solvent	yield (%) <sup>b</sup>	trans:cis <sup>c</sup>	ee (%) <sup>d</sup>
1	MeC <sub>6</sub> H <sub>5</sub>	72	99:01	90
2	ClC <sub>6</sub> H <sub>5</sub>	92	99:01	91
3	THF	29	88:12	76
4	CH <sub>2</sub> Cl <sub>2</sub>	61	99:01	85
5	CH <sub>3</sub> CN	58	96:04	84

<sup>a</sup> Performed at rt for 20 h using 1 mol % of [Co(I)] under N<sub>2</sub> with 1.0 equiv of alkene and 1.2 equiv of *t*-BDA in the presence of 0.5 equiv of DMAP; [alkene] = 0.25 M. <sup>b</sup> Isolated yields. <sup>c</sup> The trans:cis ratios were determined by GC. <sup>d</sup> The ee of trans isomer was determined by GC or HPLC on chiral stationary phase.

have different reactivity characteristics from the previously reported Cu(I)- or Rh(II)<sub>2</sub>-based systems. Efforts are underway to further improve the substrate generality, product selectivity, and process practicality of the catalytic system.

**Acknowledgment.** We are grateful to UTK and USF (Startup Funds), ACS-PRF (AC Grant), NSF (CAREER Award), and NSF (CRIF:MU-0443611, Mass Facility) for financial support.

**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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JA0746130