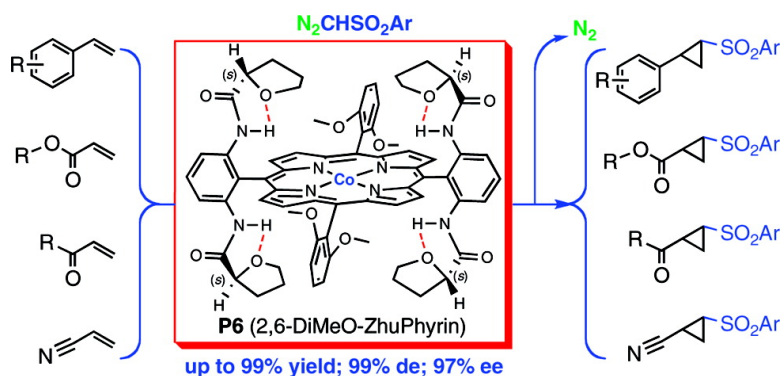


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Cobalt-Catalyzed Asymmetric Cyclopropanation with Diazosulfones: Rigidification and Polarization of Ligand Chiral Environment via Hydrogen Bonding and Cyclization

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Cyclopropane derivatives are a unique class of compounds with fundamental importance of being the smallest all-carbon cyclic molecules as well as having practical significance as recurring units in numerous natural products and as valuable synthons for many chemical transformations.¹ Of different methods, metal-catalyzed cyclopropanation of alkenes with diazo reagents is considered one of the most versatile methods for the stereoselective construction of the three-membered ring structures.^{1,2} Among known catalytic systems,^{1,2} Cu-,³ Rh-,⁴ and Ru-⁵catalyzed asymmetric processes have been successfully developed to permit olefin cyclopropanation in high yields and high selectivities. While the vast majority of those catalytic systems employed diazocarbonyls, mostly diazoacetates, as carbene sources, metal-catalyzed asymmetric cyclopropanation reactions with other types of diazo reagents are underdeveloped.¹⁻⁵

Following our original discovery of [Co(Por)]'s unique catalytic capability for cyclopropanation,^{6a,7} a family of *D*₂-symmetrical chiral porphyrins was designed and synthesized via a versatile, modular approach for the development of the asymmetric variant of the Co-catalyzed process.^{6b} Among them, [Co(**P1**)] (Figure 1) has proved to be one of the most selective catalysts for asymmetric cyclopropanation of both electron-sufficient (styrene derivatives)^{6c} and electron-deficient (α,β -unsaturated carbonyls and nitriles)^{6d} olefins with diazoacetates. To further augment its substrate generality, we decided to explore the effectiveness of the Co-based catalytic system for asymmetric cyclopropanation with diazo reagents, rather than diazoacetates. As a result of this effort, we wish to describe herein a highly effective catalytic system for asymmetric cyclopropanation employing diazosulfones. This is a class of known diazo reagents that has not been previously employed for asymmetric cyclopropanation except via a Cu-based intramolecular system reported by Nakada and co-workers.⁸⁻¹¹ Asymmetric olefin cyclopropanation with diazosulfones would be highly desirable as the resulting cyclopropyl sulfones have found a variety of applications.⁸⁻¹³

Under the conditions optimized for asymmetric cyclopropanation with diazoacetates,⁶ which required a substoichiometric amount of DMAP due to a positive trans effect,¹⁴ our initial attempts to apply [Co(**P1**)] as a catalyst to cyclopropanate styrene with tosyl diazomethane met with surprising disappointment (Table 1, entry 1). Concurring with the assumption of a competitive carbene transfer to DMAP, removal of DMAP resulted in a dramatic increase of the cyclopropane formation but still exhibited poor enantioselectivity (entry 2). Employment of a bulkier ligand **P2** bearing *meso*-2,6-dimethoxyphenyl groups improved the enantioselectivity substantially (entry 3). Alteration of the chiral units with acyclic amides but possessing intramolecular O \cdots H–N hydrogen bonding interactions provided chiral porphyrins **P3** and **P4** (Figure 1),¹⁵ Co complexes of which [Co(**P3**)] and [Co(**P4**)] gave better results than the respective [Co(**P1**)] and [Co(**P2**)] (entries 2–5). To create an even more rigid and polar chiral environment, the combined incorporation of intramolecular O \cdots H–N hydrogen bonding interactions and cyclic

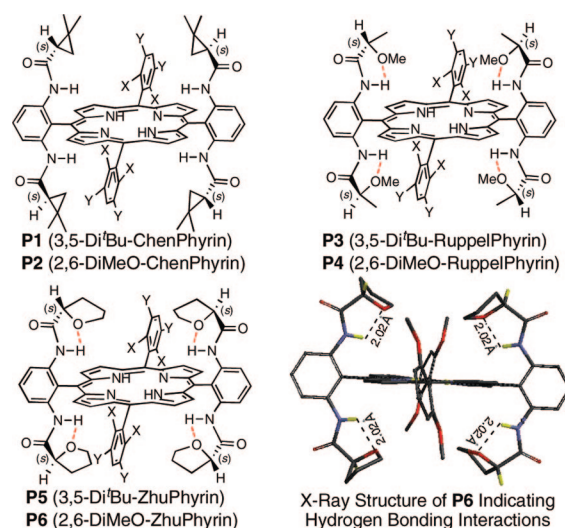


Figure 1. Structures of *D*₂-symmetrical chiral porphyrins.

Table 1. Asymmetric Cyclopropanation of Styrene with N₂CHTs Catalyzed by Cobalt(II) Complexes of Different Chiral Porphyrins^a

entry	[Co(Por)] ^b	DMAP ^c	yield (%) ^d	trans:cis ^e	ee (%) ^f	config ^g
1	[Co(P1)]	+	~6 ^h	>99:01	3	[1 <i>R</i> ,2 <i>S</i>]-(-)
2	[Co(P1)]	-	86	>99:01	14	[1 <i>S</i> ,2 <i>R</i>]-(+)
3	[Co(P2)]	-	78	>99:01	56	[1 <i>S</i> ,2 <i>R</i>]-(+)
4	[Co(P3)]	-	60	>99:01	23	[1 <i>S</i> ,2 <i>R</i>]-(+)
5	[Co(P4)]	-	99	>99:01	61	[1 <i>S</i> ,2 <i>R</i>]-(+)
6	[Co(P5)]	-	30	>99:01	54	[1 <i>R</i> ,2 <i>S</i>]-(-)
7	[Co(P6)]	-	99	>99:01	92	[1 <i>R</i> ,2 <i>S</i>]-(-)

^a Performed in CH₂Cl₂ at room temperature for 24 h using 1 mol % of [Co(Por)] under N₂ with 1.0 equiv of styrene and 1.2 equiv of N₂CHTs; [styrene] = 0.25 M. ^b See Figure 1 and Scheme S1 for structures and syntheses. ^c With (+) or without (-) 0.5 equiv of DMAP. ^d Isolated yields. ^e Determined by NMR. ^f Trans isomer ee was determined by chiral HPLC. ^g Absolute configuration of major enantiomer determined by X-ray crystal structural analysis and optical rotation. ^h Estimated by NMR.

structures led to the design and synthesis of chiral porphyrins **P5** and **P6** through the use of (*S*)-(-)-2-tetrahydrofurancarboxamide (Figure 1). This design strategy was evidenced by X-ray crystallographic analysis (Figure 1). While [Co(**P5**)] provided a better enantioselectivity than the respective [Co(**P1**)] and [Co(**P3**)] (entry 6), [Co(**P6**)] proved to be the optimal catalyst, furnishing the desired product in 99% yield and 92% ee (entry 7). Varying with enantioselectivity, all the catalysts exhibited excellent diastereoselectivity (entries 1–7). It was noted that [Co(**P5**)] and [Co(**P6**)] gave a sense of asymmetric induction opposite that of the other catalysts, despite having the same (*S*) absolute configuration (Table 1).

Table 2. [Co(P6)]-Catalyzed Diastereo- and Enantioselective Cyclopropanation of Different Alkenes with Various Diazosulfones^a

entry	olefin	cyclopropane	y (%) ^b	t:c ^c	ee (%) ^d	[α] ^e
1 ^f			99 (66) ^g	>99:01 (>99:01) ^h	92 (>99) ^h	(-) ^k
2 ^g			81	>99:01	95	(-) ^k
3 ^g			97	>99:01	96	(-)
4 ^g			99	>99:01	90	(-)
5 ^g			57	>99:01	94	(-)
6 ^g			72	>99:01	95	(-)
7 ^g			88	>99:01	95	(-)
8 ^g			77	>99:01	96	(-)
9 ^g			81	>99:01	93	(-)
10 ^h			96	94:06	89	(-)
11 ⁱ			64	>99:01	97	(-)
12 ^h			72	>99:01	90	(-)
13 ^h			93 (81) ^j	>99:01 (>99:01) ^j	89 (98) ^j	(-)
14 ^h			81	79:21	61	(-)

^a See footnote of Table 1. ^b Isolated yields. ^c The cis:trans ratio determined by NMR. ^d The trans isomer ee was determined by chiral HPLC. ^e Sign of optical rotation. ^f In CH₂Cl₂ at room temperature for 24 h using 1 mol % of [Co(P6)]. ^g In CH₂Cl₂ at -20 °C for 48 h using 1 mol % of [Co(P6)]. ^h In ClC₆H₅ at room temperature for 24 h using 2 mol % of [Co(P6)]. ⁱ In ClC₆H₅ at -20 °C for 24 h using 2 mol % of [Co(P6)]. ^j After one recrystallization. ^k [1R,2S] absolute configuration; see Table 1. ^l Ms: 4-methoxybenzenesulfonyl; Ns: 4-nitrobenzenesulfonyl.

In addition to cyclopropanation of styrene with N₂CHTs, [Co(P6)] was shown to be a general catalyst for a range of aromatic and electron-deficient terminal olefins and with different diazoarylsulfones (Table 2).¹⁶ For example, N₂CHMs and N₂CHNs served equally well as carbene sources as compared to N₂CHTs (entries 2–4). Both aromatic olefins with different substituents (entries 5–9) and electron-deficient olefins, such as α,β-unsaturated esters (entries 10–12), ketones (entry 13), and nitriles (entry 14), could be effectively cyclopropanated with N₂CHTs by [Co(P6)]. Except for the case of an α,β-unsaturated nitrile (entry 14), all the corresponding cyclopropyl sulfones were formed in high enantioselectivity and excellent trans diastereoselectivity (Table 2). Cyclopropyl sulfones that are almost enantiomerically pure (>98% ee) were obtained through a simple recrystallization procedure due to the high crystalline nature of this class of compounds, as exemplified in the styrene and methyl vinyl ketone reactions (entries 1 and 13).

In summary, we have designed and synthesized a new chiral porphyrin P6 with enhanced rigidity and polarity of chiral environment as a result of both intramolecular hydrogen bonding interactions and the use of cyclic structures. With P6 as a supporting ligand, we have demonstrated that [Co(P6)] is a highly effective

catalyst for asymmetric olefin cyclopropanation with diazosulfones. The new catalytic system is general and can be applied to various aromatic olefins as well as electron-deficient olefins, leading to high-yielding formations of the corresponding cyclopropyl sulfones in both high diastereoselectivity and high enantioselectivity. Furthermore, the [Co(P6)]-based asymmetric cyclopropanation can be operated effectively in a one-pot fashion with alkenes as limiting reagents and requires no slow addition of diazo reagents. This practical protocol is atypical for many other catalytic cyclopropanation systems, due to the competitive carbene dimerization side reaction,^{1,2} but is a common feature for [Co(Por)]-catalyzed cyclopropanation.⁶

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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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