Trans Effect on Cobalt Porphyrin Catalyzed Asymmetric Cyclopropanation

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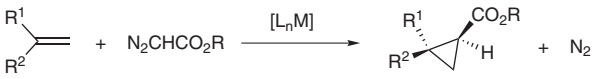
Abstract: A significant *trans* effect of potential coordinating additives was found in asymmetric cyclopropanation catalyzed by Co(II) complexes of D_2-symmetric chiral porphyrins [Co(**1**)]. Among different additives, substoichiometric amounts of DMAP resulted in substantial increases in both diastereoselectivity and enantioselectivity. A related solvent effect on the catalytic system was also observed.

Key words: cyclopropanation, chiral porphyrins, cobalt, *trans* effect, asymmetric catalysis

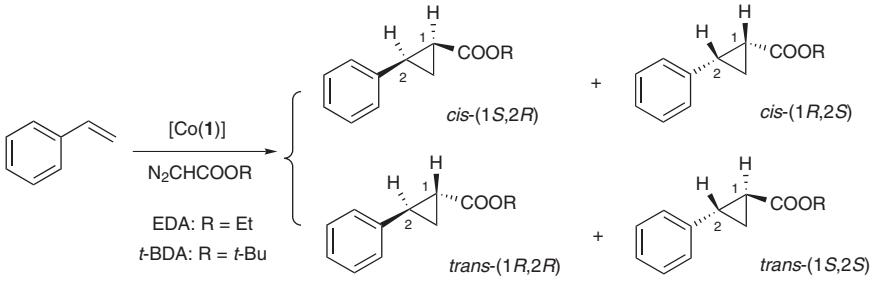
Transition-metal-complex-catalyzed asymmetric cyclopropanation of alkenes with diazo reagents represents a fundamental transformation with practical importance (Equation 1).[1] Among the various metal complexes as catalysts,[2] metalloporphyrins have received considerable attention due to the unique ligand environment, metal coordination mode, and their biological relevance to the cytochrome P-450 family of monooxygenases, which are well known to catalyze the analogous oxo-transfer processes.[3] Porphyrin complexes of several Group 8B metals (Rh, Fe, Ru, and Os) represent early examples of catalysts for cyclopropanation and related carbene transfers.[4–6] Despite the apparent periodic relationship and low cost of Co precursors, porphyrin complexes of Co ([Co(Por)]) had not been previously demonstrated for catalyzing carbene transfer reactions such as cyclopropanation.[7]



Equation 1

Recent results from us[8] and others[9] have suggested that [Co(Por)] are, in fact, highly effective catalysts for carbene transfer processes. More importantly, we have shown that [Co(Por)]-based catalytic systems including cyclopropanation can be operated effectively in one-pot fashion with alkenes as limiting regents, requiring no slow-addition of diazo reagents.[8] In addition to achieving significant asymmetric induction, Co-catalyzed cyclopropanation can be tailored into a *trans*- or *cis*-selective system through employment of appropriate chiral porphyrin ligands. Using styrene as an example (Scheme 1), it was demonstrated that each of the four possible stereoisomers could be formed as the dominant product with the use of Co(II) complexes of the appropriate D_2-symmetric chiral porphyrin [Co(**1**)] (Figure 1).[8d] During the study, we have revealed a significant *trans* effect of potential coordinating additives on the [Co(Por)]-based cyclopropanation, which we wish to disclose in detail in this report.

The *trans* effect was systematically investigated for the cyclopropanation of styrene as the standard substrate with ethyl diazoacetate (EDA) and *tert*-butyl diazoacetate (*t*-BDA) as carbene sources. Three different D_2-symmetric chiral cobalt porphyrins [Co(**1a**)], [Co(**1b**)], and [Co(**1c**)] were used as the catalysts (Figure 1), effectively prepared from the same bromoporphyrin synthon via palladium-mediated one-pot, quadruple amidation reactions with the corresponding chiral amide building blocks.[8d] Using 1 mol% catalyst loading, the cyclopropanation was typically carried out at room temperature using styrene as the limiting reagent and 1.2 equivalents of EDA or *t*-BDA. As summarized in Table 1, upon addition of 0.5 equivalent of pyridine, both diastereoselectivity and enantioselectivity for the EDA reaction by [Co(**1a**)] were significantly im-



Scheme 1 Asymmetric cyclopropanation of styrene.

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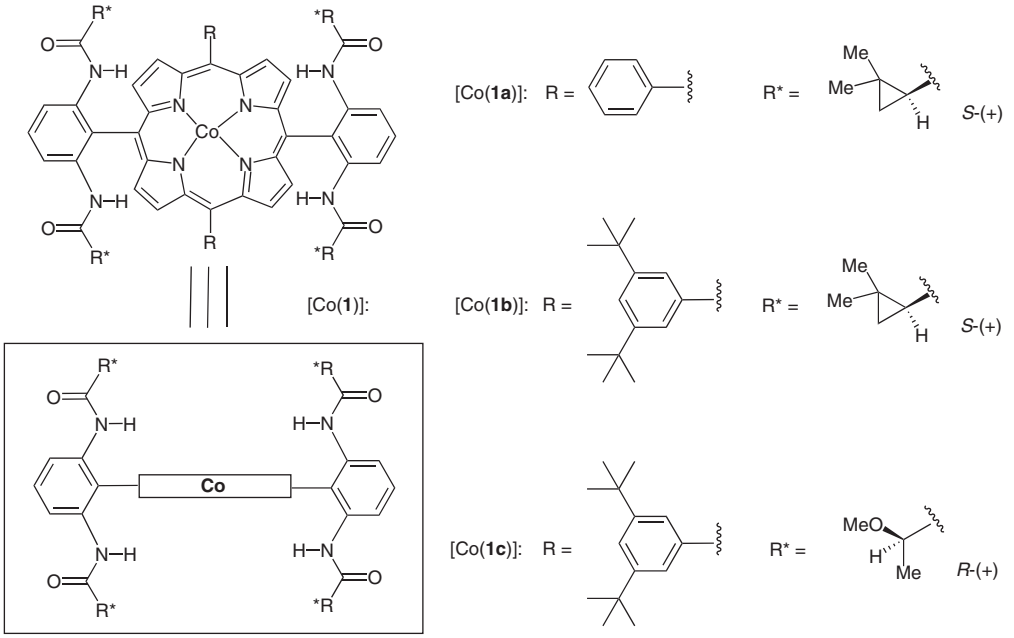

Figure 1 Structures of D_2-symmetric chiral cobalt porphyrins.

proved while retaining high yields (entries 1 and 2). The selectivities were further enhanced with *N*-methylimidazole as the additive (entry 3). The best selectivities were obtained by adding 0.5 equivalent of 4-(dimethylamino)pyridine (DMAP) (entry 4). Although a slight increase of enantioselectivity was detected in the case of triphenylphosphine, no effects were observed for additives such as triphenylphosphine oxide and 2,6-lutidine (entries 5–7), presumably due to their poorly coordinative nature. When *t*-BDA was used for the reaction, the positive effect of DMAP was further amplified to afford 88% ee and 98% de for the *trans* isomer (entry 8). Together, these results imply possible in situ formation of five-coordinate Co(II) catalysts when in the presence of certain additives that are superior catalysts in comparison with the initial four-coordinate Co(II) precursors.

Cobalt–porphyrin complex [Co(**1b**)], where the two nonchiral meso-groups are 3,5-di-*tert*-butylphenyl instead of phenyl (Figure 1), was found to be a generally more selective catalyst for cyclopropanation (entries 1, 9, and 18). In combination with the positive *trans* effect of DMAP, employment of [Co(**1b**)] afforded even better selectivities for both EDA and *t*-BDA reactions (entries 10 and 19). These results were further improved when the reactions were performed at a lower temperature (entries 11 and 20). In the case of *t*-BDA, 98% ee and >98% de were obtained for the cyclopropanation of styrene (entry 20). While both diastereoselectivity and enantioselectivity were essentially unaffected, increasing the equivalent of DMAP from the substoichiometric to stoichiometric or excess amounts resulted in the lower product yields (entries 12 and 13), suggesting partial inhibition of the catalyst. Presumably, both active sites on the catalyst were occupied with excess DMAP, forming a high percentage of catalytically inactive species. A similar situation might be responsible for the observed solvent effect on the catalytic process. Though reactions run in many other solvents gave similar results to those in toluene, the use of coordinating solvents, such as THF, caused a dramatic decrease in product yields (entries 14–17).

[Co(Por)]-catalyzed cyclopropanation is one of the few catalytic systems that can be either *trans*-selective or *cis*-selective using the same metal ion while changing the environment of the ligand system. As both [Co(**1a**)] and [Co(**1b**)] are *trans*-selective catalysts, the use of [Co(**1c**)], where the chiral building block is a less compact acyclic amide (Figure 1), afforded the *cis*-dominant products (entries 21–27). Although no obvious effect on the *cis*/*trans* ratio was observed for the [Co(**1c**)]-catalyzed cyclopropanation with EDA, addition of 0.5 equivalent of DMAP significantly improved the enantioselectivity of the major *cis*-products but reduced the yield (entries 21 and 22). As in the case of [Co(**1b**)] (entries 14–17), similar solvent effects were observed for the [Co(**1c**)]-catalyzed reactions (entries 23–26).

In summary, we have revealed in detail a significant *trans* effect of additives with potential coordinative capabilities for asymmetric cyclopropanation of styrene by chiral Co(II) porphyrins. Through the systematic study, DMAP in substoichiometric amounts was identified to have the largest positive effect on [Co(**1**)]-based catalytic systems, resulting in substantial increases in both diastereoselectivity and enantioselectivity. The study may suggest the superior catalytic capability of potential five-coordinate Co(II) complexes, which might be formed in situ and in equilibrium with the initial four-coordinate Co(II) precursor.

Table 1 *Trans* Effect on Asymmetric Cyclopropanation of Styrene Catalyzed by D_2-Symmetric Chiral Cobalt Porphyrins [Co(**1**)][a]

Entry	[Co(**1**)][b]	Diazo Comp	Solvent	Additive (equiv)[c]	Yield (%)[d]	*trans*/*cis*[d]	ee (%)[e]	Config[f]
1	[Co(**1a**)]	EDA	toluene	none	92	87:13	31	1*R*,2*R*
2	[Co(**1a**)]	EDA	toluene	pyridine (0.5)	92	96:04	55	1*R*,2*R*
3	[Co(**1a**)]	EDA	toluene	*N*-methylimidazole (0.5)	84	97:03	59	1*R*,2*R*
4	[Co(**1a**)]	EDA	toluene	DMAP (0.5)	91	96:04	67	1*R*,2*R*
5	[Co(**1a**)]	EDA	toluene	Ph_3P (0.5)	61	84:16	42	1*R*,2*R*
6	[Co(**1a**)]	EDA	toluene	Ph_3PO (0.5)	87	89:11	34	1*R*,2*R*
7	[Co(**1a**)]	EDA	toluene	2,6-lutidine (0.5)	89	89:11	33	1*R*,2*R*
8	[Co(**1a**)]	*t*-BDA	toluene	DMAP (0.5)	85	99:01	88	1*R*,2*R*
9	[Co(**1b**)][g]	EDA	toluene	none	89	88:12	43	1*R*,2*R*
10	[Co(**1b**)]	EDA	toluene	DMAP (0.5)	86 (82)[h]	97:03	78	1*R*,2*R*
11	[Co(**1b**)]	EDA	toluene	DMAP (0.5)[i]	86	98:02	83	1*R*,2*R*
12	[Co(**1b**)]	EDA	toluene	DMAP (1.0)	63	96:04	77	1*R*,2*R*
13	[Co(**1b**)]	EDA	toluene	DMAP (2.0)	50	96:04	76	1*R*,2*R*
14	[Co(**1b**)][g]	EDA	PhCl	none	91	88:12	32	1*R*,2*R*
15	[Co(**1b**)][g]	EDA	CH_2Cl_2	none	75	90:10	28	1*R*,2*R*
16	[Co(**1b**)][g]	EDA	MeCN	none	91	87:13	46	1*R*,2*R*
17	[Co(**1b**)][g]	EDA	THF	none	20	82:18	40	1*R*,2*R*
18	[Co(**1b**)]	*t*-BDA	toluene	none	22	92:08	67	1*R*,2*R*
19	[Co(**1b**)]	*t*-BDA	toluene	DMAP (0.5)	88 (84)[h]	>99:01	95	1*R*,2*R*
20	[Co(**1b**)]	*t*-BDA	toluene	DMAP (0.5)[i]	84 (85)[h]	>99:01	98	1*R*,2*R*
21	[Co(**1c**)]	EDA	toluene	none	90	32:68	50	1*S*,2*R*
22	[Co(**1c**)]	EDA	toluene	DMAP (0.5)	65 (59)[h]	31:69	92	1*S*,2*R*
23	[Co(**1c**)]	EDA	PhCl	none	99	36:64	52	1*S*,2*R*
24	[Co(**1c**)]	EDA	CH_2Cl_2	none	91	40:60	61	1*S*,2*R*
25	[Co(**1c**)]	EDA	MeCN	none	73	46:54	76	1*S*,2*R*
26	[Co(**1c**)]	EDA	THF	none	25	45:55	72	1*S*,2*R*
27	[Co(**1c**)][j]	*t*-BDA	toluene	DMAP (0.5)	78 (75)[h]	37:63	96	1*S*,2*R*

[a] Carried out at r.t. for 17–20 h under N_2 using 1.0 equiv of styrene, 1.2 equiv of diazo reagent, and 1 mol% catalyst with 0.25 M of [styrene].
[b] See Figure 1 for structures of cobalt porphyrins.
[c] The equivalent was relative to styrene used.
[d] Determined by GC.
[e] Enantiomeric excess of major enantiomer determined by chiral GC.
[f] Absolute configuration of major enantiomer determined by optical rotation.
[g] Used 2 mol% catalyst with 0.13 M of [styrene].
[h] Yields in parentheses represent isolated yields.
[i] Carried out at –20 °C for 8 h.
[j] Used 5 mol% catalyst.

All reactions were carried out under N_2 in oven-dried glassware following standard Schlenk techniques. THF and toluene were distilled under N_2 from sodium benzophenone ketyl. Other anhyd solvents were purchased from Aldrich. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Varian Mercury 300 spectrometer and referenced with respect to internal TMS standard or residual solvent. GC-MS analysis was performed on a Hewlett-Packard G

1800B GCD system equipped with a CP-Chirasil-Dex CB or a B-DM column.

Cyclopropanation of Styrene; General Procedure

Catalyst [Co(**1**)] (1 mol%) was placed in an oven-dried, resealable Schlenk tube. The tube was capped with a Teflon screw cap, evacuated, and backfilled with N_2. The screw cap was replaced with a rubber septum, and styrene (0.25 mmol, 1 equiv) was added via syringe, followed by solvent (0.5 mL), the appropriate diazo compound (1.2 equiv), and again solvent (0.5 mL). The tube was purged with N_2 for 1 min and then the septum was replaced with the Teflon screw cap. The tube was sealed and its contents were stirred at constant temperature. After completion of the reaction, *n*-tridecane was added as an internal standard and the crude product was analyzed by GC-MS. The cyclopropanes were purified by flash chromatography on silica gel and their structures confirmed by NMR spectroscopy.

Ethyl 2-Phenylcyclopropane-1-carboxylate[7,8]

***trans*-Isomer**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.09–7.31 (m, 5 H), 4.17 (q, *J* = 7.2 Hz, 2 H), 2.52 (ddd, *J* = 9.3, 6.6, 4.2 Hz, 1 H), 1.90 (ddd, *J* = 8.7, 5.4, 4.5 Hz, 1 H), 1.60 (ddd, *J* = 9.0, 5.1, 4.2 Hz, 1 H), 1.30 (ddd, *J* = 8.4, 6.6, 4.8 Hz, 1 H), 1.28 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 173.4, 140.1, 128.4, 126.4, 126.1, 60.7, 26.2, 24.2, 17.1, 14.3.

***cis*-Isomer**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.18–7.28 (m, 5 H), 3.88 (q, *J* = 7.2 Hz, 2 H), 2.59 (m, 1 H), 2.08 (ddd, *J* = 9.0, 7.8, 5.6 Hz, 1 H), 1.72 (ddd, *J* = 6.3, 4.9, 4.4 Hz, 1 H), 1.32 (ddd, *J* = 8.9, 7.9, 5.0 Hz, 1 H), 0.97 (t, *J* = 7.2 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.9, 136.5, 129.2, 127.8, 126.6, 60.1, 25.4, 21.7, 14.0, 11.1.

***tert*-Butyl 2-Phenylcyclopropane-1-carboxylate[7,8]**

***trans*-Isomer**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.07–7.29 (m, 5 H), 2.44 (m, 1 H), 1.82 (m, 1 H), 1.53 (m, 1 H), 1.46 (s, 9 H), 1.21 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 172.5, 140.5, 128.4, 126.3, 126.0, 80.5, 28.1, 26.0, 25.3, 17.0.

***cis*-Isomer**

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.17–7.27 (m, 5 H), 2.52 (m, 1 H), 1.99 (m, 1 H), 1.65 (m, 1 H), 1.24 (m, 1 H), 1.13 (s, 9 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 170.1, 136.8, 129.5, 127.8, 126.5, 80.0, 27.7, 25.0, 22.7, 10.5.

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