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Bromoporphyrins as Versatile Synthons for Modular Construction of Chiral Porphyrins: Cobalt-Catalyzed Highly Enantioselective and Diastereoselective Cyclopropanation

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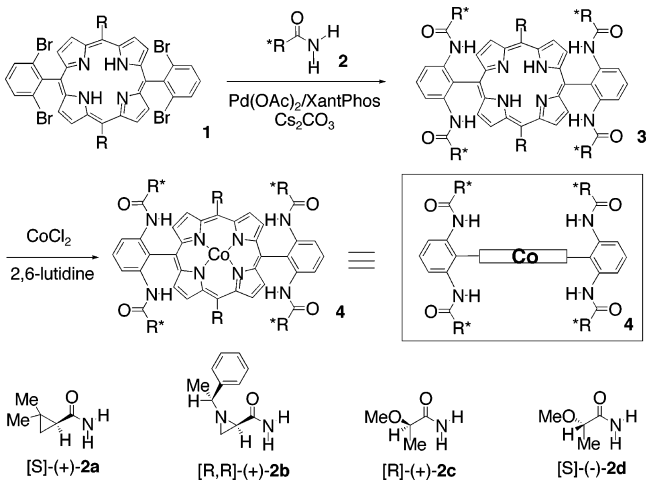
Metalloporphyrins have been found to catalyze a range of fundamentally and practically important chemical transformations, some of which represent the first demonstrations of such catalytic processes.[1] The most notable examples include an array of atom/group-transfer reactions such as oxene (epoxidation and hydroxylation), nitrene (aziridination and amination), and carbene (cyclopropanation and carbene insertion) transfers.[1,2] Due to the unique ligand environment and metal coordination mode, unusual reaction selectivities and excellent catalyst turnovers have been observed for metalloporphyrin-based catalysts. Since the first application of a chiral iron porphyrin complex for catalytic asymmetric epoxidation,[3] a number of chiral porphyrins have been synthesized as potential asymmetric catalysts.[4] Although significant progress has been made, catalytic reactions based on metalloporphyrins have not been developed into practical methodologies that can be used in asymmetric synthesis. This can mainly be attributed to the expense and difficulty associated with chiral porphyrin synthesis.

Among different approaches for chiral porphyrin synthesis,[4] the most general and chirally economic scheme is to covalently attach suitable chiral building blocks to a preformed porphyrin synthon at specific peripheral positions that possess functional groups. Successful synthons include *meso*-tetrakis(2-aminophenyl)porphyrin,[5] *meso*-tetrakis(2,6-diaminophenyl)porphyrin,[6] *meso*-tetrakis(2,6-dihydroxyphenyl)porphyrin,[7] and *meso*-tetrakis(2,6-dicarboxyphenyl) porphyrin,[8] which allow attachments with chiral acids, amines, or alcohols through amide or ester bond formation. To enhance the synthetic utility and flexibility of metalloporphyrin-based asymmetric catalysis, it is desirable to develop alternative synthons to be used for versatile construction of chiral porphyrins that could be employed in practical asymmetric catalysis.

Within this context, we recently demonstrated that bromoporphyrins are versatile precursors for syntheses of heteroatom-functionalized porphyrins via metal-catalyzed carbon−heteroatom cross-coupling reactions with soft, non-organometallic nucleophiles.[9] These syntheses can be achieved under mild conditions with a wide range of amines,[9a,b] amides,[9d] alcohols,[9c] and thiols,[9e] leading to a family of novel porphyrins with otherwise inaccessible heteroatom functionalities in high yields. Considering the ready availability of chiral amines, amides, alcohols, and thiols, these synthetic methodologies render bromoporphyrins as a new class of synthons for the synthesis of chiral porphyrins. In this Communication, we report that 5,10-bis(2′,6′-dibromophenyl)porphyrins are versatile synthons for modular construction of chiral porphyrins via palladium-catalyzed amidation reactions with chiral amides. The quadruple carbon−nitrogen bond formation reactions can be accomplished in high yields with different chiral amide building blocks under mild conditions, forming a family of D_2-symmetric chiral porphyrins (Scheme 1). Cobalt(II) complexes of these chiral porphyrins were shown to be active catalysts for highly enantioselective and diastereoselective cyclopropanation under a practical one-pot protocol (alkenes as limiting reagents and no slow addition of diazo reagents).

Scheme 1. Synthesis of Chiral Porphyrins and Cobalt Complexes



A series of 5,15-bis(2,6-dibromophenyl)porphyrins, **1a**−**k**, containing different *meso*-aryl and -alkyl R groups at the 10 and 20 positions, which were readily prepared by MacDonald [2+2] porphyrin synthesis using Lindsey's condition,[10] were successfully coupled with several optically pure amides **2a**−**d** under palladium-catalyzed amidation conditions[9d] (Scheme 1 and Table 1). The combination of $Pd(OAc)_2$ and XantPhos could effect the quadruple amidation reactions of synthons **1a**−**k** with chiral amides **2a**−**d** to deliver a family of D_2-symmetric chiral porphyrins **3a**−**p** in high yields (Table 1). The nearly perpendicular arrangement between the *meso*-phenyl ring and the porphyrin plane, in combination with the *trans*-amide conformation, should direct the *ortho*-chiral R* units toward the center of porphyrins (Scheme 1), as suggested from the observed large high-field NMR chemical shifts of the chiral R* units. As a result, high asymmetric induction may be achieved for catalytic reactions with metal complexes of these chiral porphyrins. Through the combined use of the chiral R* and *meso*-R groups, it may be possible to control diastereoselectivity as well as enantioselectivity.

Cobalt complexes of chiral porphyrins **4a**−**p**, which were prepared in high yields (Scheme 1 and Table 1), were applied as catalysts for cyclopropanation using styrene as a model substrate (Table 2).[11] Using 1 mol % **4**, the reactions proceeded effectively at room temperature in one pot with styrene as the limiting reagent, producing the desired cyclopropanes in high yields (Table 2). Each of the four possible stereoisomers (*trans*-(1*R*,2*R*), *trans*-(1*S*,2*S*), *cis*-(1*S*,2*R*), or *cis*-(1*R*,2*S*)) could be produced as the dominant product when **4a**, **4b**, **4c**, or **4d** was used as the catalyst, respectively (entries 1−4). This notable result signifies a high dependence of catalytic selectivity on the structure of the chiral R* units. The moderate

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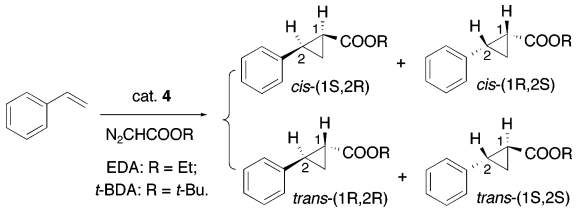
Table 1. Synthesis of Chiral Porphyrins **3** and Cobalt Complexes **4**[a]

entry	R	1	2	3, yield (%)[a]	4, yield (%)[a]
1	Ph	**1a**	**2a**	**3a**, 78	**4a**, 88
2	Ph	**1a**	**2b**	**3b**, 64	**4b**, 86
3	Ph	**1a**	**2c**	**3c**, 75	**4c**, 95
4	Ph	**1a**	**2d**	**3d**, 71	**4d**, 95
5	4-*t*-BuPh	**1b**	**2a**	**3e**, 86	**4e**, 72
6	4-CF_3Ph	**1c**	**2a**	**3f**, 77	**4f**, 95
7	pentaFPh	**1d**	**2a**	**3g**, 46	**4g**, 86
8	4-acetylPh	**1e**	**2a**	**3h**, 66	**4h**, 83
9	2,4,6-triMePh	**1f**	**2a**	**3i**, 84	**4i**, 91
10	2,6-diMeOPh	**1g**	**2a**	**3j**, 59	**4j**, 95
11	3,5-diMeOPh	**1h**	**2a**	**3k**, 88	**4k**, 96
12	3,5-di-*t*-BuPh	**1i**	**2a**	**3l**, 85	**4l**, 91
13	3,5-di-*t*-BuPh	**1i**	**2c**	**3m**, 79	**4m**, 96
14	3,5-di-*t*-BuPh	**1i**	**2d**	**3n**, 72	**4n**, 92
15	4-*n*-heptyl	**1j**	**2a**	**3o**, 74	**4o**, 95
16	H	**1k**	**2a**	**3p**, 79	**4p**, 91

[a] See Supporting Information for details. [b] Yields represent isolated yields of >95% purity as determined by ^{1}H NMR.

Table 2. Asymmetric Cyclopropanation of Styrene Catalyzed by **4**[a]



entry	4	diazo	additv	yield (%)[b]	trans:cis[b]	ee (%)[c]	config[d]
1	**4a**	EDA		92 (−)	87:13	31	1*R*,2*R*
2	**4b**	EDA		77 (−)	66:34	35	1*S*,2*S*
3	**4c**	EDA		92 (−)	32:68	48	1*S*,2*R*
4	**4d**	EDA		95 (−)	32:68	51	1*R*,2*S*
5	**4a**	EDA	DMAP	91 (−)	96:04	67	1*R*,2*R*
6	**4c**	EDA	DMAP	52 (−)	44:56	88	1*R*,2*R*
7	**4d**	EDA	DMAP	57 (−)	42:58	89	1*R*,2*R*
8	**4l**	EDA	DMAP	86 (82)	97:03	78	1*R*,2*R*
9	**4l**	*t*-BDA	DMAP	88 (84)	>99:01	95	1*R*,2*R*
10[e]	**4l**	*t*-BDA	DMAP	84 (85)	>99:01	98	1*R*,2*R*
11	**4m**	EDA	DMAP	65 (59)	31:69	92	1*S*,2*R*
12[f]	**4m**	*t*-BDA	DMAP	78 (75)	37:63	96	1*S*,2*R*
13	**4n**	EDA	DMAP	68 (−)	30:70	94	1*R*,2*S*
14[f]	**4n**	*t*-BDA	DMAP	76 (−)	38:62	95	1*R*,2*S*
15	**4o**	EDA	DMAP	80 (−)	96:04	59	1*R*,2*R*
16	**4o**	*t*-BDA	DMAP	73 (−)	99:01	78	1*R*,2*R*

[a] Reactions were carried out at room temperature in toluene for 20 h under N_2 with 1.0 equiv of styrene, 1.2 equiv of diazo reagent, and 1 mol % **4** in the presence of 0.5 equiv of additive. Concentration: 0.25 mmol styrene/mL of toluene. [b] Determined by GC. Yields in parentheses represent isolated yields. [c] ee of major diastereomer determined by chiral GC. [d] Absolute configuration of major enantiomer determined by optical rotation. [e] Carried out at −20 °C for 8 h. [f] 5 mol % **4** was used.

enantioselectivities were doubled when 0.5 equiv of 4-(dimethylamino)pyridine (DMAP) was added (entries 5−7), suggesting significant trans influence of potential coordinate ligands on the metal center. The DMAP additive also boosted the production of the trans isomer (entries 5−7). Further improvements in diastereoselectivity and enantioselectivity were observed when **4a** was replaced with **4l**, where the two *meso*-groups are 3,5-di-*tert*-butylphenyl instead of phenyl (entry 8). When *t*-BDA was used, the same catalyst produced the *trans*-(1*R*,2*R*)-isomer as the only diastereomer in 95% ee, which was further improved to 98% ee at −20 °C (entries 9 and 10).[12] The same structure modification resulted in 96% ee for the *cis*-(1*S*,2*R*)-isomer with **4m** and 95% ee for the *cis*-(1*R*,2*S*)-isomer with **4n** (entries 12 and 14). The results obtained with **4o** bearing *meso*-*n*-heptyl groups (entries 15 and 16) further underline the importance of both R and R* groups of the chiral porphyrins **4** in achieving high selectivities.

In summary, we have demonstrated that the readily accessible 5,10-bis(2′,6′-dibromophenyl)porphyrins are versatile synthons for modular construction of chiral porphyrins via palladium-catalyzed multiple amidation reactions with chiral amides. Cobalt(II) complexes of the D_2-symmetric chiral porphyrins are shown to be active catalysts for highly enantioselective and diastereoselective cyclopropanation under a practical one-pot protocol. We are currently working to expand the applications of this family of chiral porphyrins in various asymmetric catalytic processes.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(12) It is reasonable to expect that the same results would be obtained for the *trans*-(1*S*,2*S*)-isomer if the enantiomer of **4l** is employed as a catalyst.

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