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Free Bases of Chiral *N*-Substituted Porphyrins as Catalysts for Asymmetric Reaction

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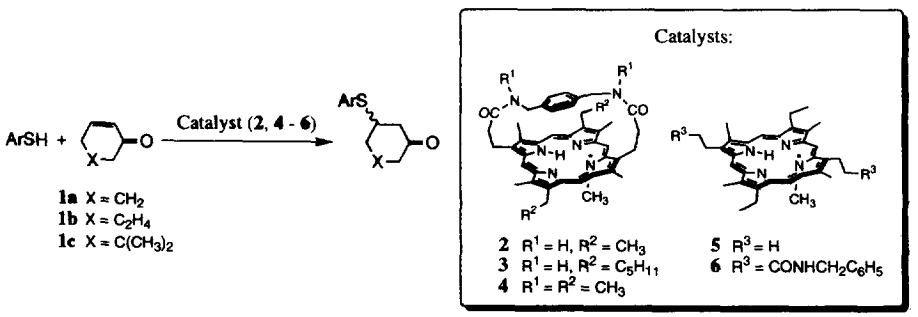
Abstract: Chiral *N*-substituted porphyrin free bases having a conformationally locked asymmetric nitrogen atom catalyzed Michael addition of thiophenols to cycloalkenones, where the reaction proceeded enantioselectively when the catalyst having a xylylene strap anchored via two secondary amido linkages (**2**) was employed.

Metal complexes of chiral porphyrins have attracted increasing attention in recent years not only from a biological viewpoint[1] but also as new chiral auxiliaries and receptors for asymmetric reactions and recognition.[2,3] We have succeeded in optical resolution and absolute structure determination of a variety of chiral porphyrins and metalloporphyrins.[4] Herein we report the first example of an asymmetric reaction catalyzed by chiral porphyrin free bases. The catalysts employed here (**2** and **4** - **6**) are chiral *N*-methylated porphyrins, in which the methylated core nitrogen atom forms a chiral center due to the presence of two different substituents at the pyrrole-β positions together with the out-of-plane conformation of the *N*-methyl group.[5]

The reaction examined here is the Michael addition of thiophenols (ArSH) to cycloalkenones (**1**) (Scheme).[6] Among the catalysts examined (**2** and **4** - **6**), a chiral *N*-methylmesoporphyrin II having a xylylenedi-*sec*-amido strap (**2**)[3a] was the most effective in terms of both catalytic activity and enantioselectivity. For example, the reaction of 4-*tert*-butylthiophenol (297 equiv.) and 2-cyclohexenone



Scheme Michael addition of thiophenols to 2-cycloalkenones (**1**) catalyzed by chiral free-base *N*-substituted porphyrins (**2**, **4** - **6**). Structures of the (*S*)-catalysts.

Table. Asymmetric Michael Addition of Thiophenols (ArSH) to Cycloalkenones (**1**) Catalyzed by Chiral Free-base *N*-Methylporphyrins (**2**, **4** - **6**). [a]

Run	Catalyst	ArSH / Ar	Cycloalkenone	*T* / °C	*t* / days	Conv. / % [b]	[*R*] / [*S*] [c]
1	(*S*) -**2**	C_6H_5	**1a**	-40	2	>99	73.5 / 26.5
2	(*S*) -**2**	2-$C_{10}H_7$	**1a**	-40	6	>99	67.5 / 32.5
3	(*S*) -**2**	2-$MeOC_6H_4$	**1a**	-40	19	88	76.5 / 23.5
4	(*S*) -**2**	4-$MeOC_6H_4$	**1a**	-40	3	95	71.5 / 28.5
5	(*R*) -**2**	2-ClC_6H_4	**1a**	-40	6	>99	31.5 / 68.5
6	(*S*) -**2**	2-MeC_6H_4	**1a**	-40	6	>99	77.5 / 22.5
7	(*R*) -**2**	4-MeC_6H_4	**1a**	-40	5	96	32.5 / 67.5
8	(*R*) -**2**	2,6-$Me_2C_6H_3$	**1a**	-40	22	72	21.0 / 79.0
9	(*R*) -**2**	5-Bu^t-2-MeC_6H_3	**1a**	-40	21	80	22.5 / 77.5
10 [d]	(*S*) -**2**	C_6F_5	**1a**	-40	6	>99	50.0 / 50.0
11	(*S*) -**2**	4-$Bu^tC_6H_4$	**1a**	-40	8	97	75.5 / 24.5
12 [d]	(*S*) -**2**	4-$Bu^tC_6H_4$	**1a**	-40	15	>99	71.5 / 28.5
13	(*S*) -**2**	4-$Bu^tC_6H_4$	**1a**	-10	3	96	72.0 / 28.0
14	(*R*) -**2**	4-$Bu^tC_6H_4$	**1a**	-40	8	>99	26.5 / 73.5
15	(*S*) -**2**	4-$Bu^tC_6H_4$	**1b**	-40	17	96	71.0 / 29.0
16	(*S*) -**2**	4-$Bu^tC_6H_4$	**1c**	-10	53	93	72.0 / 28.0
17	(*R*) -**4**	4-$Bu^tC_6H_4$	**1a**	-10	29	36	50.0 / 50.0
18	(*S*) -**5**	4-$Bu^tC_6H_4$	**1a**	-10	30	89	42.0 / 58.0
19	(*R*) -**5**	4-$Bu^tC_6H_4$	**1a**	-10	56	94	58.5 / 41.5
20	(*S*) -**6**	4-$Bu^tC_6H_4$	**1a**	-40	3	92	50.0 / 50.0

[a] A typical experimental procedure: To a suspension of catalyst (3.7 μmol) in dry toluene (2.5 mL) containing naphthalene (30 mg, GC standard) was added ArSH (1,100 μmol) under argon, and the mixture was stirred for 30 min at 50 °C to give a homogeneous solution containing a protonated catalyst. Cycloalkenone (370 μmol) was added at -78 °C to this flask, and the content was stirred at -40 or -10 °C. The reaction was monitored by GC, and the pseudo first-order rate constant (*k*) was calculated. The product was isolated by silica gel chromatography with hexane, then CH_2Cl_2 as eluents. No reaction took place in the absence of *N*-substituted porphyrins. [b] Conversion of **1** by GC. [c] From ^{13}C NMR of the corresponding (2*R*, 3*R*)-butanediol acetals (ref. 6). [d] Using 370 μmol of ArSH and 1,100 μmol of **1a**.

(**1a**) (100 equiv.) in toluene catalyzed by **2** (1.5 mM) with (*S*)-configuration at the asymmetric nitrogen atom[7] proceeded at -40 °C to 62 and 97 % conversion in 1 and 8 days (pseudo first-order rate constant (k) = 4.9 x 10^{-4} dm^3 mol^{-1} s^{-1}), to give 3-(4'-*tert*-butylthiophenyl)-cyclohexanone in 74 % isolated yield, with the [*R*] / [*S*] ratio, as determined from the corresponding (2*R*, 3*R*)-butanediol acetal,[8] of 75.5 / 24.5 (run 11, Table). As expected, use of a catalyst with the opposite configuration ((*R*)-**2**) for the same reaction resulted in preferential formation of the (*S*)-isomer in comparable enantioselectivity ([*R*] / [*S*] = 26.5 / 73.5) (run 14). At a higher temperature such as -10 °C, the reaction proceeded more rapidly (k = 1.5 x 10^{-3} dm^3 mol^{-1} s^{-1}) without any significant decrease in enantioselectivity (run 13). Asymmetric Michael addition of other thiophenols such as non-substituted and methyl-, methoxy-, chloro-, and *tert*-butyl-substituted thiophenols, and 2-naphthalenethiol to **1a** also occurred in the presence of (*R*)- or (*S*)-**2** (runs 1 - 9), where (*R*)-**2** always afforded (*S*)-products preferentially, and *vice versa*. The highest enantioselectivity ([*R*] / [*S*] = 21.0 / 79.0) was observed for the reaction of sterically hindered 2,6-dimethylthiophenol (run 8), while use of highly acidic pentafluorothiophenol resulted in no enantioselection (run 10). A higher cycloalkenone such as **1b** showed a similar reactivity to **1a** in the reaction with 4-*tert*-butylthiophenol (run 15), while the reaction of sterically hindered **1c** proceeded rather sluggishly but enantioselectively (run 16).

In these reactions, the catalysts promote deprotonation from thiophenols to generate arylthiolate anions as nucleophiles: When 2-chlorothiophenol was added to a toluene solution of (*R*)-**2**, and the mixture was heated at 50 °C for 10 h, the electronic absorption spectrum was clearly changed to a characteristic pattern of mono-protonated *N*-substituted porphyrins,[5] and this protonation also caused a considerable change in the circular dichroism (CD) spectrum,[9] as observed with acetic acid as a proton donor.

The structure of the catalyst strongly affects the catalytic activity and enantioselectivity: When the ring-opened analogue of **2** having two flexible *sec*-amido functionalities (**6**) was used as catalyst,[10] the reaction of 4-*tert*-butylthiophenol to **1a** proceeded more rapidly (k =1.1 x 10^{-3} dm^3 mol^{-1} s^{-1}) than in the case with **2**, but no enantioselection occurred (run 20). When the amido NH functionalities in **2** were methylated (**4**), the reaction was extremely slow even upon elevating the temperature to -10 °C (run 17).[11] A similar low catalytic activity was observed for the non-strapped catalyst having alkyl groups in place of *sec*-amido functionalities (**5**), where a very slow reaction occurred at -10 °C (k = 7.0 x 10^{-6} dm^3 mol^{-1} s^{-1}) to give a Michael product in a low enantioselectivity (runs 18 and 19). In this case, although the reaction was negligible at -40 °C, external addition of a secondary amide such as *N*-acetylbenzylamine promoted the reaction.[12] However, even in the presence of a large excess of the external amide (100 equiv. with respect to **5**), the catalytic activity of **5** (k = 1.2 x 10^{-6} dm^3 mol^{-1} s^{-1}) was much lower than that of **2** or **6**.

From the above observations, it is evident that the "built-in" amido NH functionalities in **2** plays an essential role in activation of substrates and stereochemical control of the reaction. ^{1}H NMR studies in toluene-d_8 on a mixture of **3** (2.3 mM) and **1a** (4.6 mM) at -40 °C showed clear upfield shifts for the signals due to the vinylic protons of **1a** (δ 6.10 → 5.97 (2-H) and δ 6.30 → 6.18 (3-H)).[13] Furthermore, upon titration of a toluene solution of **3** (10 mM) with **1a** at room temperature, a new amide NH stretching IR band, assignable to a hydrogen-bonded NH, appeared at 3,322 cm^{-1} ($\Delta\nu$ = -100 cm^{-1}) and grew at the expense of the original absorption at 3,422 cm^{-1}, while the pyrrolic NH absorption at 3,295 cm^{-1} remained intact. More interestingly, the change in the absorbance at 3,422 cm^{-1} relative to that at 3,295 cm^{-1} became levelled off at about 0.5 after the ratio **[1a] / [3]** exceeded 100.[14] From these observations, it is likely that enones are hydrogen-bonded with either of the two amido NH functionalities in **2**,[15] and activated for the nucleophilic attack of arylthiolates. Such a hydrogen-bonding interaction may also lead to a shielding of one of the enantiotopic faces in the enone by the bulky porphyrin moiety, in which the rigid conformation of the amido linkages in **2** plays a role, considering the lack of stereoselection with **6** having flexible *sec*-amido functionalities (run 20).

In conclusion, we have demonstrated asymmetric Michael addition catalyzed by chiral *N*-substituted porphyrin free bases, and have shown a potential utility of porphyrins for organic synthesis.

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7. The absolute configurations at the asymmetric nitrogen atoms in **2** - **6** were deduced from their CD profiles based on the CD - absolute structure correlation for a crystallographically defined chiral *N*-substituted etioporphyrin I.[4c]
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9. UV-VIS and CD data (toluene, room temperature): (*R*)-**2** (0.2 mM), UV-VIS: λ_{max}/nm = 412, 505, 533, 587, 645; CD: λ/nm ([Θ] x 10^{-4}/deg cm^2 dmol^{-1}) = 430 (-2.0), 401 (9.7). (*R*)-**2** / 2-chlorothiophenol (0.2 / 180 mM) after heated at 50 °C for 10 h, UV-VIS: λ_{max}/nm = 406.5, 542.5, 570.5; CD: λ/nm ([Θ] x 10^{-4}/deg cm^2 dmol^{-1}) = 423 (-1.1), 401 (9.7), 378 (5.1), 314 (1.0).
10. Prepared from (*S*)-**2** by acidolysis of the strap amido linkages followed by amidation with benzylamine: HRMS (FAB): m/z 759.4378 [(M+H)$^+$, calc. for $C_{49}H_{54}N_6O_2$, 759.4387]; UV-VIS ($CHCl_3$): λ_{max}/nm (ε/dm^3 mmol^{-1} cm^{-1}) = 643 (5.89), 587 (6.03), 536 (7.08), 507 (14.5), 410 (115); ^{1}H NMR ($CDCl_3$) δ 9.99, 9.89, 9.86 (3s, 4H, *meso*), 6.6 - 7.0 (m, overlapped, 10H, $C_6H_5CH_2$), 5.40 (br, 2H, $C_6H_5CH_2$), 5.05 (br, 2H, $C_6H_5CH_2$), 4.5 - 3.7 (m, overlapped, 10H, porph-CH_2CH_3, porph-CH_2CH_2CO, porph-CH_2CH_2CO), 3.58, 3.51, 3.48 (3s, 9H, porph-CH_3), 3.15 (br, overlapped, 5H, amide-NH, porph-CH_3), 2.44 (m, 2H, porph-CH_2CH_2CO), 1.87 (t, 6H, porph-CH_2CH_3), -3.25 (br, 1H, pyrrolic NH), -4.75 (s, 3H, *N*-CH_3).
11. Prepared from (*R*)-**2** by lithiation with $(Me_3Si)_2NLi$ followed by treatment with CH_3I: HRMS (FAB): m/z 709.4222 [(M+H)$^+$, calc. for $C_{45}H_{53}N_6O_2$, 709.4230]; UV-VIS ($CHCl_3$): λ_{max}/nm (ε/dm^3 mmol^{-1} cm^{-1}) = 645 (3.98), 588 (3.72), 532 (3.89), 505 (11.5), 412 (89.1). No further methylation at the pyrrolic NH was confirmed by ^{1}H NMR from the relative signal intensity of pyrrolic *N*-Me (δ -4.6 - -4.2, 3H) to *meso*-H (δ 9.5 - 10.2, 4H).
12. No reaction took place with *N*-acetylbenzylamine alone in the absence of *N*-substituted porphyrins under similar conditions.
13. **3** with an improved solubility was used in place of **2** for spectroscopic studies. Synthesis of the precursor strapped porphyrin has been reported: Konishi, K.; Oda, K.; Nishida, K.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* **1992**, 114, 1313.
14. IR (toluene, room temperature): A_{3422} / A_{3295} ([**1a**] / [**3**]) = 1.0 (0), 0.84 (0.5), 0.47 (1.0), 0.47 (1.5), 0.48 (2.5).
15. Stereospecific hydrogen-bonding interactions between the strap *sec*-amido functionalities and *Z*-amino acids have been reported for a zinc complex of **2** in chiral recognition.[3c]

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