Asymmetric Catalysis

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Helical Chiral Pyridine *N*-Oxides: A New Family of Asymmetric Catalysts**

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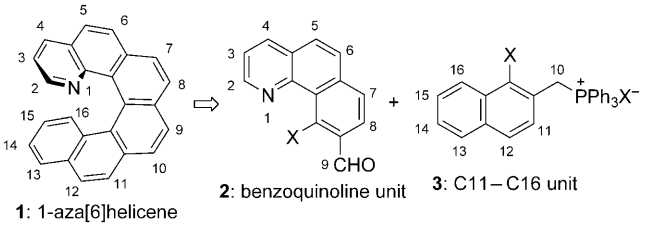
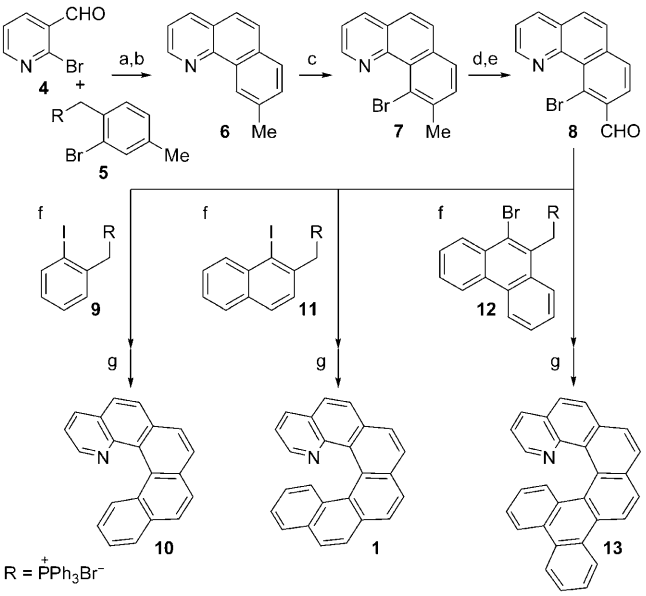
The design, synthesis, and study of new catalyst structures have had an enormous impact on chemical synthesis, and continue to be a central challenge in asymmetric catalysis.[1] We recently described that a 2-aminopyridinium ion might be a promising catalaphore[2] for the design of new asymmetric hydrogen-bond donor catalysts.[3] In that connection, we became interested in 1-aza[6]helicene[4] **1** as a chiraphore[2] because a first-order analysis of the crystal structure of an analogous 1,16-diaza[6]helicene[5] suggests that its pyridine ring is well-desymmetrized in terms of both top-from-bottom and left-from-right differentiations. To our knowledge, the application of **1** and analogous helical chiral pyridines[5–7] in asymmetric catalysis has not been studied, even though **1** has been known in the literature since 1975.[4d] In this context, we were prompted to develop an efficient synthesis of 1-azahelicenes, which allows systematic structural variation—important for the elucidation of the relationship between catalyst structure, reactivity, and selectivity—and to exploit them as chiraphores. In view of the utility of helical chiral pyridines such as **1**, it occurred to us that the corresponding pyridine *N*-oxides might prove to be effective asymmetric catalysts.[8] Herein, we describe the scalable synthesis of 1-azahelicenes and the structural characterization of the corresponding *N*-oxides, and we apply this new family of compounds to the catalytic enantioselective desymmetrization of *meso* epoxides (see Table 1). This study provides the first report of the application of azahelicenes in asymmetric catalysis.[9]

An examination of the structure of **1** suggests that the chiral environment in the vicinity of the nitrogen atom can be tuned by structural modification at cabon atoms 11–16. Therefore, we devised a convergent synthetic route to **1** in which benzoquinoline unit **2** and C11–C16 unit **3** could be expeditiously united (Scheme 1). This strategy would allow ready access to the necessary 1-azahelicene derivatives by simply replacing **3** with its readily available structural analogues, such as **9** and **12** (Scheme 2). Preparation of key unit **8** starts from commercially available pyridine **4** and phosphonium salt **5**, which was readily synthesized in three steps from commercially available 2-bromo-4-methyl benzaldehyde. The highly *Z*-selective Wittig reaction[6b,10] of **4** and **5** and subsequent Stille–Kelly reaction[5,11] provided benzoquinoline **6**. The catalytic C–H functionalization method developed by Sanford and co-workers[12] readily converted **6** into **7** from which **8** was obtained in an ordinary way. The second sequence of the highly *Z*-selective Wittig reaction and the Stille–Kelly reaction of **8** with **9**, **11**, or **12** provided 1-azahelicenes **10**, **1**, or **13**, respectively. The scalability of this



Scheme 1. Synthesis design.



Scheme 2. Syntheses of 1-azahelicenes: a) NaHMDS, DMF, 78%; b) $[PdCl_2(Ph_3P)_2]$, $(Me_3Sn\text{-})_2$, PhMe, 77%; c) Pd(II) catalyst,[12] NBS, CH_3CN, 84%; d) benzoyl peroxide, NBS, PhH, 71%; e) 2-nitropropane, NaOEt, EtOH, DMF, 86%; f) NaHMDS, DMF, 79% for **9**, 76% for **11**, 62% for **12**; g) $[PdCl_2(Ph_3P)_2]$, $(Me_3Sn\text{-})_2$, PhMe, 70% for **10**, 61% for **1**, 55% for **13**. HMDS = 1,1,1,3,3,3-hexamethyldisilazane; DMF = *N*,*N*-dimethylformamide; NBS = *N*-bromosuccinimide.

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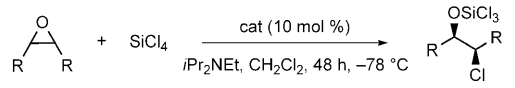
route was demonstrated by synthesizing **1** on a 2.0 gram scale. Oxidation of **10**, **1**, or **13** with *meta*-chloroperbenzoic acid furnished the desired pyridine *N*-oxides, **14**–**16**, respectively, in 32–49% yields,[13] the enantiomers of which were readily resolved by chiral HPLC methods (Table 1).

Table 1: Desymmetrization of *meso* epoxides by helical-chiral pyridine *N*-oxides.[a]



Entry		(*P*)-**14**	(*P*)-**15**	(*P*)-**16**
1	Ph, Ph	77% yield 93% *ee*	80% yield 92% *ee*	77% yield 94% *ee*
2	Ar, Ar Ar = 2-naphtyl	79% yield 81% *ee*	77% yield 73% *ee*	76% yield 92% *ee*
3	R, R R = $BnOCH_2$	71% yield 49% *ee*	68% yield 42% *ee*	72% yield 65% *ee*
4		70% yield 0% *ee*	68% yield 22% *ee*	74% yield 33% *ee*

[a] All data are the average of two runs. Both *P* and *M* catalysts were used but only *P* catalysts are shown for clarity.

As a test for our catalyst, we examined the effectiveness of helical chiral catalyst design in the catalytic desymmetrization of *meso* epoxides with chlorosilanes, a reaction first studied by Denmark and co-workers and then by the groups of Fu, Nakajima, Kim, and Chelucci.[14] All three compounds (*P*)-**14**–**16** were found to sufficiently catalyze the ring-opening reaction of *cis*-stilbene oxide by $SiCl_4$ and provided the corresponding (*R*,*R*)-chlorohydrin with high *ee* values (Table 1, entry 1). For the three catalsyts, the ring opening proceeded in better enantioselectivity for substrates having aromatic substituents rather than for those bearing alkyl groups (Table 1, entries 1 and 2 versus 3 and 4). Catalyst **14** provided better *ee* values than **15** for acyclic epoxides (Table 1, entries 1–3), but the opposite was true for the cyclic epoxide (Table 1, entry 4). Overall, **16** was found to be better in terms of enantioselectivity than **14** and **15**, and is comparable to the best catalysts in the literature[14] for both aromatic- and alkyl-substituted epoxides. The scope of the present reaction was additionally probed with catalyst, **16** (Table 2). The enantiomeric excess of the chlorohydrin was found to be somewhat sensitive to electronic effects (Table 2, entries 1–3). The ring opening proceeded with a moderate *ee* value for an acyclic alkyl substituted epoxide (Table 2, entry 4), but with a modest *ee* value for a cyclic substrate (Table 2, entry 5).

Table 2: Desymmetrization of *meso* epoxides by **16**.[a]

Entry	R[b]	Yield [%]	*ee* [%]
1	4-ClC_6H_4	84	94
2	4-$CF_3C_6H_4$	83	92
3	4-$CH_3C_6H_4$	83	87
4	$CH_2O(CH_2)_3Ph$	63	72
5	-CH_2OCH_2-	64	33

[a] All data are the average of two runs. Both *P* and *M* catalysts were used. [b] R reprsents groups appended to *meso*-epoxide substrate (see reaction equation in Table 1).

The difference in the degree of helical deformation between the crystal structures of **14**–**16** was found to be negligible[16] (Figure 1). Also evident from these structures is

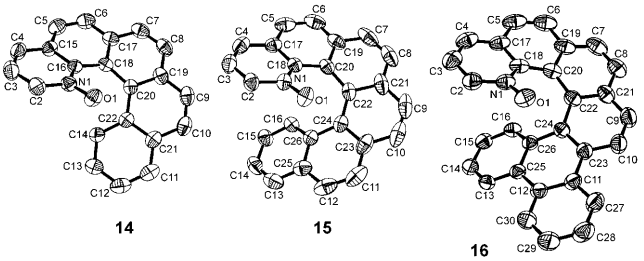


Figure 1. ORTEP views of the solid-state structures of **14**, **15** (40% probability thermal ellipsoid), and **16** (50% probability thermal ellipsoid).[15]

that the chiral space around their oxygen atoms are clearly defined by the rings beneath them. Modification of these rings does indeed lead to increased enantioselectivity and substrate scope in the catalytic desymmetrization of *meso* expoxides with $SiCl_4$ (Table 1).

In summary, we have designed and synthesized a new family of chiral catalysts, helical chiral pyridine *N*-oxides, and we have applied them to the catalytic, enantioselective ring opening of *meso* epoxides. In the course of these studies, we have provided the first demonstration that the appropriate structural modification to the rings beneath the plane of the pyridine *N*-oxide can serve as a powerful means for tuning the catalyst enantioselectivity. We anticipate that this strategy would be general for the tuning of the catalyst enantioselectivity for this class of chiraphores. Ongoing studies are directed at providing support for this hypothesis and at developing additional applications of 1-azahelicenes as chiraphores for catalysis of synthetically significant transformations.

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[15] CCDC 694398 (**14**), 694399 (**15**), 694340 (**16**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. **14**: $C_{21}NOH_{13}\cdot CH_3CN$, $M_r = 336.38$, orthorhombic, $P2_12_12_1$, $a = 7.9696(3)$ Å, $b = 12.1846(5)$ Å, $c = 17.9802(7)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 1745.99(12)$ Å^3, $Z = 4$, $T = 296$ K, $Mo_{K\alpha} = 0.71073$ Å. Final $R1(F^2)$ was 0.0375 for 2332 reflections $I > 2\sigma(I)$; **15**: $C_{25}NOH_{15}$, $M_r = 345.38$, monoclinic, $P2_1/c$, $a = 11.0282(4)$ Å, $b = 10.0812(4)$ Å, $c = 15.5534(6)$ Å, $\beta = 103.313(1)°$, $V = 1682.72(11)$ Å^3, $Z = 4$, $T = 296$ K, $Mo_{K\alpha} = 0.71073$ Å. Final $R1(F^2)$ was 0.0484 for 2540 reflections $I > 2\sigma(I)$; **16**: $C_{29}NOH_{17}$, $M_r = 395.44$, orthorhombic, $Pbca$, $a = 10.3786(4)$ Å, $b = 19.1827(7)$ Å, $c = 19.4292(7)$ Å, $\alpha = \beta = \gamma = 90°$, $V = 3868.2(2)$ Å^3, $Z = 8$, $T = 296$ K, $Mo_{K\alpha} = 0.71073$ Å. Final $R1(F^2)$ was 0.0446 for 2603 reflections $I > 2\sigma(I)$.

[16] See the Supporting Information.

