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Conformationally Rigid Chiral Bicyclic Skeleton-Tethered Bipyridine *N,N′*-Dioxide as Organocatalyst: Asymmetric Ring Opening of *meso*-Epoxides

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In memory of Professor A. Srikrishna for his outstanding contribution in organic synthesis.

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Abstract: The conformationally rigid chiral bicyclic skeleton tethered bipyridine *N,N′*-dioxide (−)-**9** has been designed, synthesized and examined as an organocatalyst in the enantioselective ring opening of *meso*-epoxides using tetrachlorosilane ($SiCl_4$). The catalyst (−)-**9** is found to exhibit good enantioselectivity for substituted *cis*-stilbene epoxides; whereas, the saturated cyclic *meso*-epoxides display a moderate enantioselectivity. At −30 °C in chloroform, the catalyst (−)-**9** with 0.5 mol% loading generated the chlorohydrins in up to 97% yield with up to 93% *ee*. The possible creation of transient axial chiral environment around hypervalent silicon species due to the presence of conformationally rigid chiral bicyclic skeleton tethered bipyridine *N,N′*-dioxide may be responsible for such enantioselectivity observed in the desymmetrization of *meso*-epoxides.

Keywords: asymmetric synthesis; catalyst design; chiral bipyridine *N,N′*-dioxide; desymmetrization of *meso*-epoxides; organocatalysis

The stereoselective ring opening of oxiranes with nucleophiles such as carbon, nitrogen, oxygen, halogen, etc., generates products with two contiguous stereogenic centers of diverse functional groups: alcohols, amino alcohols, alkoxy alcohols, diols, halohydrins etc.[1] Andrews et al., and Fu et al. introduced the Lewis base-catalyzed ring opening of epoxides with chloride as nucleophile to generate chlorohydrins.[2] Based on this method Denmark et al.[3] reported the ring opening of epoxides with chloride as nucleophile under the influence of chiral phosphoramides as a Lewis base to generate non-racemic chlorohydrins. This observation resulted in the introduction of other types of Lewis base catalysts such as phosphine oxides[4] and *N*-oxides[5–10] for enantioselective ring opening of *meso*-epoxides.

Since then, different types of chiral pyridine *N*-oxides **a–f** (Figure 1) have been introduced by several groups, including those of Fu et al.,[5] Nakajima et al.,[6] Chelucci et al.,[7] Takenaka et al.,[8] Malkov et al.,[9] and Kotora et al.,[10] to effect the desymmetri-

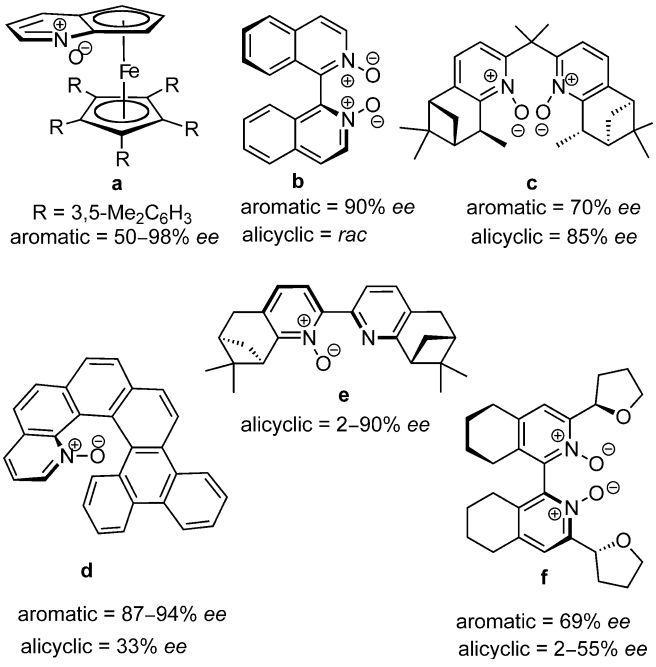


Figure 1. Chiral pyridine *N*-oxides for asymmetric ring opening of *meso*-epoxides.

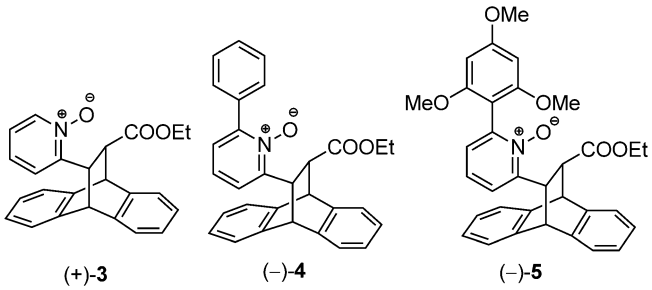


Figure 2. CRCB skeleton-attached pyridine *N*-oxides.

zation of *meso*-epoxides. The enantioselectivity in the desymmetrization of *meso*-epoxides is realized due to the presence of chiral elements such as planar chirality, axial chirality, central chirality, helical chirality as well as the combination of both axial and central chirality in organocatalysts.

All these catalysts exhibit good enantioselectivity for the ring opening of *cis*-stilbene oxides, except **c** and **e** which are moderately effective for *meso*-epoxides derived from cycloalkenes. Furthermore, the reported catalysts require very low temperatures (−78 °C to −90 °C) to exert enantioselectivity.[5–10] Thus, the design and development of a catalyst system exhibiting better enantioselectivity and efficiency for both structural classes is still warranted.

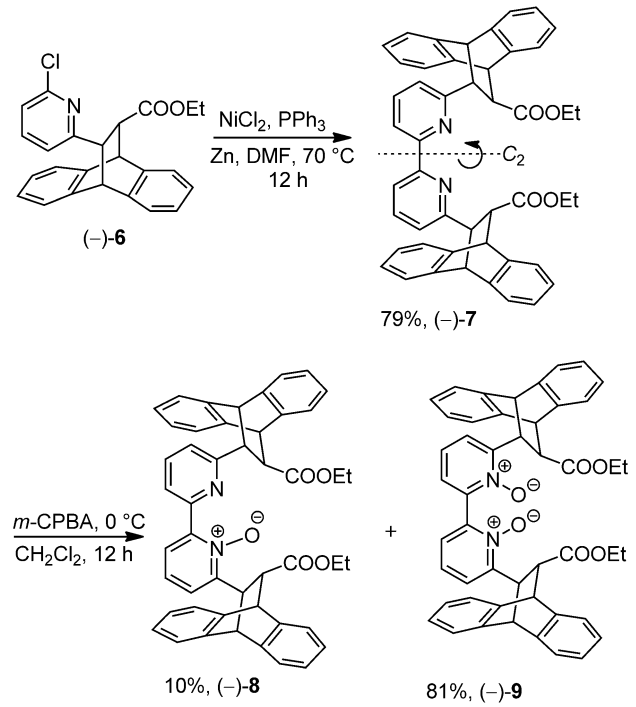
Recently, we have engineered a family of conformationally rigid chiral bicyclic (CRCB) skeleton-substituted pyridine *N*-oxides, **3**–**5**, with an appropriate stereoelectronic environment for organocatalytic enantioselective allylation of aldehydes (Figure 2).[11]

The presence of a pyridine *N*-oxide unit on the CRCB skeleton prompted us to examine this class of molecules for the enantioselective ring opening of *meso*-epoxides using $SiCl_4$. Hence, the catalysts **3**–**5** were screened for desymmetrization of *cis*-stilbene oxide, using $SiCl_4$/diisopropylethylamine at −40 °C in dichloromethane. The steric factor and nucleophilicity of the catalysts **3**–**5** dictated the reactivity as well as the enantioselectivity. The catalyst **3**, after 18 h, sucessfully generated the chlorohydrin **2a** in 32% *ee*. The reaction was very sluggish in the presence of catalyst **4** (even after 24 h only 82% conversion of **1a** was observed) and the chlorohydrin **2a** was obtained only in 5% *ee*. This may due to the presence of unfavourable nucleophilicity and steric crowding compared to the catalyst **3**. Quite interestingly, the catalyst **5** with strong nucleophilic character delivered the chlorohydrin **2a**, although only in moderate enantioselectivity (42% *ee*, 12 h).

These results prompted us to modify the catalyst structure for better selectivity. Even though the catalyst **f**, reported by Kotora et.al,[10] possess both axial and central chirality, the enantioselectivities obtained in the desymmetrization of *meso*-epoxides were found to be moderate. *Is this because of the presence of permanent axial and central chiralities disfavouring the formation of an appropriate chiral environment around the hypervalent silicon species due to conformational restrictions? If so, would the avoidance of permanent axial chirality provide the conformational freedom around the bipyridyl N,N′-dioxide unit? This conformational freedom in bipyridine N,N′-dioxide may lead to effective bidentate coordination with $SiCl_4$. During this process, the presence of bulky stereogenic groups at the 3,3′-positions in bipyridine N,N′-dioxide may direct the generation of a transient axial chiral environment around the hypervalent silicon species.* Hence, we presume that this transient axial chiral environment may assist the enantioselective desymmetrization of *meso*-epoxides.

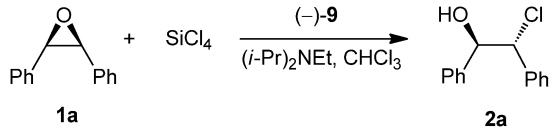
Based on this hypothesis, we have designed a C_2-symmetric bipyridine *N,N′*-dioxide (−)-**9** possessing a bulky stereogenic group, the CRCB skeleton, at the 3,3′-positions. The chiral bipyridine (−)-**7** was successfully prepared in 79% yield through biaryl coupling of the chiral molecule (−)-**6**[11a] using $NiCl_2$/PPh_3 and Zn in DMF at 70 °C for 12 h.[13] The bipyridine (−)-**7** on treatment with *m*-CPBA in dichloromethane provided both mono-*N*-oxide (−)-**8** and *N,N′*-dioxide (−)-**9** in 10% and 81% yields, respectively (Scheme 1).

Both *N*-oxides were separated through column chromatography and examined for desymmetrization of *meso*-epoxides. The catalytic efficiency as well as the enantiomeric purity of chlorohydrin **2a** generated



Scheme 1. Synthesis of bipyridine derivatives.

Table 1. Effect of catalyst loading and temperature on efficiency and enantioselectivity.[a]



1a 2a

Entry	(−)-**9** [mol%]	Temp. [°C]	Time	Conv. [%][b]	*ee* [%][c]
1	5	−40	20 min	100	85
2	2.5	−40	30 min	100	89
3	1	−40	1 h	100	89
4	0.5	−40	105 min	100	89
5	0.25	−40	5 h	100	88
6	0.1	−40	18 h	100	84
7	0.5	−60	24 h	62	74
8	0.5	−50	8 h	100	82
9	0.5	−30	70 min	100	89
10	0.5	−20	35 min	100	83

[a] All the reactions were performed with **1a** (0.25 mmol, 1 equiv.), $SiCl_4$ (1M in dichloromethane, 0.38 mL, 1.5 equiv.) with $(i\text{-Pr})_2NEt$ (5 equiv.) in the presence of various amounts of catalyst (−)-**9** in chloroform (0.8 mL) at −40 °C.

[b] Determined from ^1H NMR spectra.

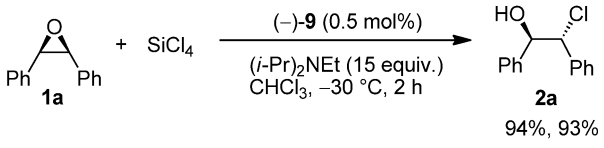
[c] Determined by chiral HPLC analysis and the product **2a** produced in all experiments is of the (1*R*,2*R*)-(−)-configuration, as revealed by a comparison of HPLC retention times.[4a]

from **1a** in the presence of (−)-**8** was not effective (after 24 h, only 45% conversion of **1a** to **2a** with 0% *ee* was observed in dichloromethane). Meanwhile, 20 mol% of catalyst (−)-**9** completely converted the epoxide **1a** to the corresponding chlorohydrin **2a** with 76% *ee* upon reaction with $SiCl_4$ and diisopropylethylamine in dichloromethane at −40 °C in just 10 min. Lower catalyst loading, for example, 5 mol% of (−)-**9** also exhibited 100% conversion in 20 min to produce **2a** in 85% *ee* (Table 1, entry 1).

With this encouraging result, the catalytic efficiency of (−)-**9** with a 5 mol% loading was examined in other commonly employed solvents, such as acetonitrile, 1,1,2,2-tetrachloroethane and 1,2-dichloroethane; the chlorohydrin **2a** was produced in 39% *ee*, 84% *ee* and 64% *ee*, respectively. Hence, chloroform is found to be an ideal solvent.[13] The decrease in catalyst loading enhanced the enantioselectivity with only a slight increase in reaction time. This observation rendered the opportunity to perform the reaction in chloroform at −40 °C by varying the catalyst (−)-**9** loading from 5 mol% to 0.1 mol% to improve the enantioselectivity (Table 1, entries 1–6). Indeed, the enantiomeric purity of the chlorohydrin **2a** produced was increased from 85% to 89% while decreasing the catalyst loading from 5 mol% to 0.5 mol%. At the same time, the reaction time required for the complete conversion also increased from 20 min at 5 mol% catalyst loading to 105 min at 0.5 mol% catalyst loading. Further lowering of catalyst loading to 0.25 and 0.1 mol% resulted in slight decreases in enantioselectivity (84% *ee* for 0.1 mol% catalyst loading) as well as drastic increases in reaction time (18 h) for complete conversion of *meso*-epoxide (Table 1, entries 5 and 6). Both 0.5 mol% and 1 mol% catalyst loading furnished the chlorohydrin in 89% *ee* at −40 °C (Table 1, entries 3 and 4). Even though 0.5 mol% of (−)-**9** required a longer reaction time (105 min) compared to 1 mol%, which required 60 min, we have chosen 0.5 mol% catalyst loading for optimization studies owing to the advantage of using a smaller amount of catalyst.

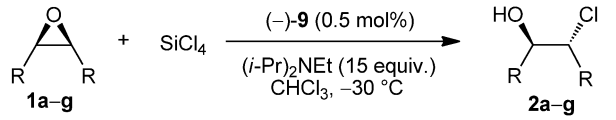
With 0.5 mol% catalyst loading the experiments were carried out at various temperatures such as −60 °C, −50 °C, −30 °C, and −20 °C to realize the better enantioselectivity (Table 1, entries 4, 7–9). The reaction at −60 °C was found to be unfavourable in terms of both rate of the reaction and the enantioselectivity (Table 1, entry 7). Gradual increases of reaction temperature from −60 °C to −30 °C were accompanied by increases in the rate of the reaction (24 h to 70 min) as well as the enantioselectivity from 74% to 89% (Table 1, entries 4, 7–9). Further increase of the reaction temperature from −30 °C to −20 °C caused a decrease in enantioselectivity from 89% *ee* to 83% *ee* (Table 1, entry 10). Therefore, the catalytic efficiency and enantioselectivity was found to be optimum at −30 °C. The quantity of base, diisopropylethylamine, is also known to exhibit crucial role in both reactivity as well as enantioselectivity. Hence, the experiments were performed with various equivalents (1 equiv. to 20 equiv.) of diisopropylethylamine in the presence of catalyst (−)-**9** (0.5 mol%) at −30 °C in chloroform.[13] This study reveals that the optimum amount of diisopropylethylamine required to realize better enantioselectivity (93% *ee*) was found to be 15 equivalents. Further increases of base equivalents decreased the rate of the reaction as well as the enantioselectivity.

Therefore, the catalyst (−)-**9** (0.5 mol%), $SiCl_4$ (1.5 equiv.), DIPEA (15 equiv.) at −30 °C in chloroform is found to be the optimized conditions for the enantioselective desymmetrization of *meso*-epoxides (Scheme 2).



Scheme 2. Optimized conditions for ring opening of *cis*-stilbene oxide.

Table 2. Desymmetrization of *meso*-epoxides with $SiCl_4$ catalyzed by (−)-**9**.[a]



Entry	R	Time [min]	Yield [%][b]	*ee* [%]	Configuration
1	C_6H_5 (**1a**)	120	94	93[c]	1*R*,2*R*[e]
2	3-CH_3O-C_6H_4 (**1b**)	90	96	89[c]	1*R*,2*R*[e]
3	4-CH_3-C_6H_4 (**1c**)	105	92	89[c]	1*S*,2*S*[e]
4	4-F-C_6H_4 (**1d**)	180	97	78[c]	1*S*,2*S*[e]
5	-$(CH_2)_3$- (**1e**)	45	67	22[d]	-[f]
6	-$(CH_2)_4$- (**1f**)	60	65	42[d]	1*R*,2*R*[g]
7	-$(CH_2)_6$- (**1g**)	90	84	69[d]	1*R*,2*R*[g]

[a] All reactions were performed with **1** (0.25 mmol, 1 equiv.), $SiCl_4$ (1M in dichloromethane, 0.38 mL, 1.5 equiv.), $(i\text{-Pr})_2NEt$ (15 equiv.) in the presence of catalyst (−)-**9** (0.5 mol%) in chloroform (0.8 mL) at −30 °C.
[b] Yields are of isolated product.
[c] The *ee* values were determined by chiral HPLC analysis.
[d] The *ee* value was established by ^{19}F NMR analysis of the corresponding Mosher's esters and the Mosher esterification was quantitative as revealed by TLC analysis and ^1H NMR spectra of the crude products, which excludes a possible *ee* amplification during this derivatization.
[e] Absolute configurations were assigned by comparing the HPLC retention time with the literature data.[4]
[f] The absolute configuration of chlorohydrin is not determined.
[g] Absolute configurations were assigned by comparing the sign of optical rotation with the literature data.[3a,12]

Based on these conditions, the versatility of catalyst (−)-**9** was evaluated for the enantioselective ring opening of *meso*-epoxides of various structural classes at −30 °C in chloroform (Table 2). The substituted *cis*-stilbene oxides, **1b–d**, generated the corresponding chlorohydrins, **2b–d**, in excellent yields, 92–97%, with good enantioselectivities, 78–89% (Table 2, entries 2–4). The efficiency of the catalyst (−)-**9** was further examined for the ring opening of cyclic *meso*-epoxides such as cyclopentene oxide, cyclohexene oxide and cyclooctene oxide using $SiCl_4$. All these substrates successfully produced the corresponding chlorohydrins **2e–g** in moderate yields with moderate enantioselectivity in short reaction times at −30 °C in chloroform (Table 2, entries 5–7). One of the challenging substrates, cyclooctene oxide **1g** successfully furnished the corresponding chlorohydrin **2g** in 84% yield with 69% *ee*. Based on the observation as reported by Malkov et al.,[9] we have examined the efficiency of mono *N*-oxide (−)-**8** (0.5 mol%) for ring opening of cyclooctene oxide **1g** using $SiCl_4$ and found it to produce **2g** in 43% yield with 5% *ee* after 36 h at −30 °C.[13]

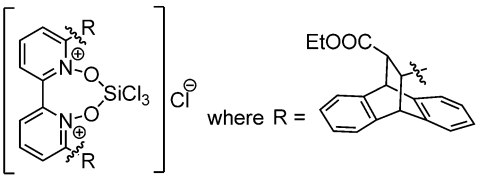


Figure 3. Proposed coordination of *N,N′*-dioxide with $SiCl_4$.

The enantioselectivity and differences in the rate of desymmetrization reaction of *cis*-stilbene oxide effected by the catalysts **4**, **5** and **9**, intrigued us to speculate the possible coordination of catalyst and substrate with $SiCl_4$ in the transition state. The rate of desymmetrization of *cis*-stilbene oxide in the presence of **4** (20 mol%) was found to be very slow (only 82% conversion even after 24 h). A similar rate could have been prevailed with catalyst (−)-**9**, because the nucleophilicity of both *N*-oxides might have been reduced inductively by each other and hence overall. On the contrary, the conversion of *cis*-stilbene oxide in the presence of (−)-**9** (20 mol%) was very fast (10 min for 100% conversion).[13] This observation may be rationalized through the involvement of bidentate coordination of *N,N′*-dioxide with $SiCl_4$ (Figure 3) and hence the creation of a transient axial chiral environment around the silicon species to exert the enantioselectivity in desymmetrization of *meso*-epoxides.

In summary, we have successfully designed a bipyridine *N,N′*-dioxide with chiral substituents at the 3,3′-positions exhibiting excellent reactivity in the desymmetrization of *meso*-epoxides using $SiCl_4$ in chloroform at −30 °C and producing chlorohydrins in up to 93% *ee*. It is interesting to note that the reaction requires only −30 °C to produce the chlorohydrins in good yield with better enantioselectivity, unlike the other reported organocatalysts that require very low temperatures (−78 °C to −90 °C) to realize a reasonable enantioselectivity. Studies on further structural modifications to get a better enantioselectivity for desymmetrization of *meso*-epoxides are progressing in this laboratory.

Experimental Section

General Experimental Procedure for the Ring Opening of *meso*-Epoxides

Tetrachlorosilane (0.38 mL, 1 M in dichloromethane, 0.38 mmol) was added dropwise to a stirred solution of epoxide (0.25 mmol), diisopropylethylamine (0.64 mL, 3.75 mmol) and bipyridine *N,N′*-dioxide (−)-**9** (0.93 mg, 0.00125 mmol) in dry chloroform (0.8 mL) at −30 °C, under a nitrogen atmosphere. After stirring for the required time, the reaction mixture was quenched with saturated aqueous solutions of KF and K_2HPO_4 (1:1, 3 mL). The organic layer was separated and then the aqueous layer was extracted

with diethyl ether (5 mL×3). The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and the solvent was evaporated on a rotary evaporator under reduced pressure. The residue was purified through silica gel column chromatography to afford the corresponding chlorohydrins.

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