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Diastereoselective synthesis of optically active rotaxane amine *N*-oxides via through-space chirality transfer

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ABSTRACT

Selective synthesis of optically active rotaxane amine *N*-oxides was achieved with high diastereoselectivity via the effective through-space chirality transfer. Oxidation of *tert*-amine moiety on axle component of rotaxane with an optically active wheel component having (*R*)-binaphthyl group was carried out. The oxidation of several rotaxanes with dimethyldioxirane was conducted in dichloromethane at −78 °C to give the corresponding amine *N*-oxides with high diastereoselectivity up to 95%, indicating the conversion via the effective through-space chirality transfer. Higher diastereoselectivity was observed with the rotaxane possessing the rigid skeleton and the *N*-benzyl substituent. The optimized structures suggested the stereochemistry of the nitrogen center of (*R*)-configuration.

Introduction

Chiral information transfer in supramolecular system has collected much attention because of the dynamic nature and the effective chirality transfer via through-space.[1] Rotaxane characterized by the mechanically linked components can undertake the through-space chirality transfer not only between the wheel and axle components for chiroptical property[2] but also between polymer backbone and its pendant rotaxane units for the induction of one-handed helix.[3] Meanwhile, the use of rotaxanes as asymmetric catalysts has been reported by controlling the dynamic nature of the components.[4] Nevertheless chiral rotaxane chemistry has been progressed, the essential meaning of rotaxane structure for the effective through-space chirality transfer has been little clarified so far. We have studied mainly the effect of the chiral wheel components on the rotaxane-related asymmetric reactions to find the important structural factors. We first demonstrated an asymmetric reaction through a Michael addition type end-cap reaction of a bulky thiol to the methacrylate axle end of a pseudorotaxane having chiral crown ether to prepare optically active rotaxane.[5] The through-space chirality transfer was certainly confirmed, although the diastereoselectivity was only 6% de, which, however, was regarded relatively high as a radical reaction involving the hydrogen abstraction as a key step for the stereogenic center determination. Further, we reported the enantioselective benzoin condensation (32% ee) with a chiral rotaxane catalyst consisting of the axle component with a thiazolium salt moiety and the crown ether wheel involving C_2 chiral binaphthyl group.[6]

Meanwhile, the modification of *sec*-ammonium function of *sec*-ammonium/crown ether-type rotaxanes as most typical ones seems a very important subject in the derivation and utilization of rotaxanes, because these rotaxanes are synthesized using hydrogen bonding between *sec*-ammonium salt and crown ether, which, however, is not necessary after the rotaxane formation. We have recently found the direct conversion of *sec*-ammonium group to *tert*-amine group as one of the modification methods.[7] We focused on the asymmetric oxidation of *tert*-amine moiety of rotaxane having a chiral crown ether wheel via through-space chirality transfer. Recently optically acitve amine *N*-oxides are used for catalytic asymmetric allylation as a chiral ligand,[8] whereas the control of *N*-central chirality of amine *N*-oxide still remains much limitation except for the case of neighboring chiral group-containing amines.[9] This Letter deals with the diastereoselective synthesis of optically active rotaxane amine *N*-oxides by direct oxidation of *tert*-amine moiety of rotaxanes (Scheme 1).

Results and discussion

Rotaxane substrates having *tert*-amine axle components and (*R*)-benzo-1,1′-binaphtho-26-crown-8-ether (BB26C8) **1**[3a] were synthesized in two steps as shown in Scheme 2. A mixture of *sec*-ammonium salt with a terminal OH group and (*R*)-BB26C8 was treated with a bulky benzoic acid in the presence of the dehydrating agent (DIC) and base (tributylphosphine) to give *sec*-ammonium/crown ether-type rotaxanes in 26–75% yields,

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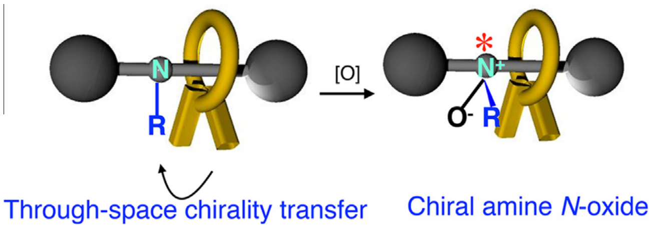
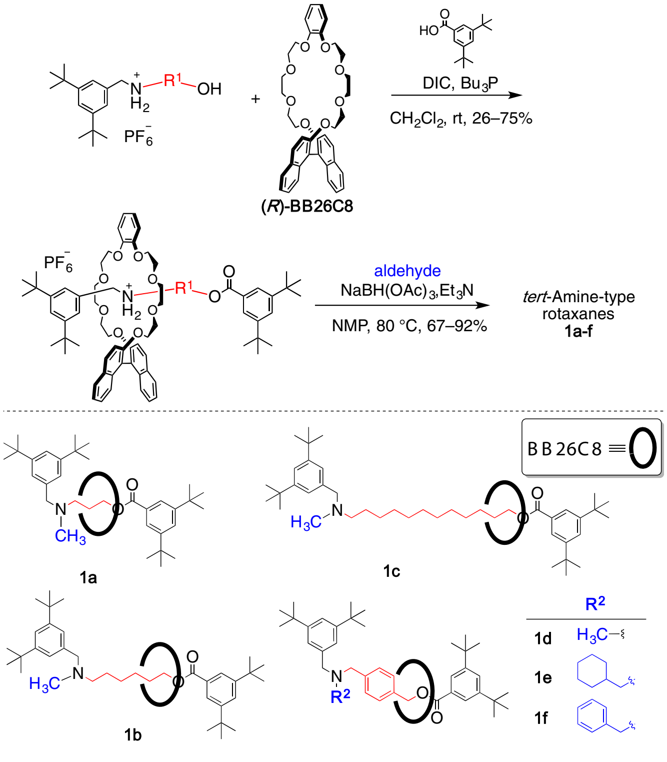


Scheme 1. Diastereoselective oxidation of *tert*-amine to amine *N*-oxide of rotaxane having a chiral wheel component.

according to our previously reported method.[7,10] Subsequent reductive N-alkylation of *sec*-ammonium rotaxanes with an appropriate aldehyde and sodium triacetoxyborohydride afforded *tert*-amine-type rotaxanes (**1a**–**1f**) in 67–92% yields.[7]

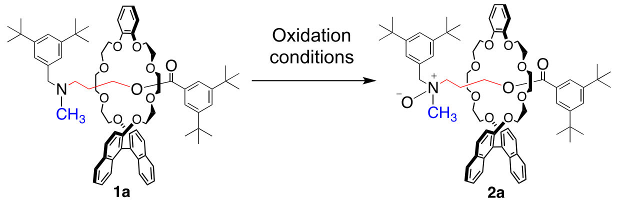
The oxidation condition was studied using rotaxane **1a** at room temperature (Table 1). With *m*-chloroperoxybenzoic acid (mCPBA),[11] no amine *N*-oxide (**2a**) was formed, probably due to the acidification of the amine moiety (entry 1). To inhibit the protonation of rotaxane substrate, the oxidation was conducted under the presence of Na_2CO_3 to afford **2a** in 26% yield (entry 2). However the reaction with *tert*-butylhydroperoxide (TBHP) also afforded no oxidation product (entry 3).[11] A small amount of **2a** was obtained with hydrogen peroxide (entry 4). Addition of a catalyst bis(acetyl acetonato)vanadium oxide ($VO(acac)_2$) as a typical catalyst (5 mol %) for TBHP enhanced the product yield to 22% (entry 5).[12] The oxidation of **1a** with dimethyl dioxirane (DMDO) formed in situ in the presence of sodium carbonate was carried out in dichloromethane to afford **2a** in 98% yield as a highly polar product (entry 6).[13] Thus, the reaction with DMDO gave the best result.

The structure **2a** was characterized by the appearance of a strong IR absorption at ca. 1000 cm^{-1} assignable to N—O bond and a down field-shifted *N*-methyl proton signal (from 1.98 to 2.18 ppm) in the ^1H NMR spectrum, in addition to the MALDI-TOF MS spectrum with the molecular ion peak of **2a** (see SI).



Scheme 2. Preparation of *tert*-amine-type rotaxanes **1**.

Table 1
Oxidation of *tert*-amine (**1a**) to amine *N*-oxide (**2a**) under various conditions



Entry	Oxidizing agent (equiv) Condition[a]	Yield (%)	de[b] (%)
1	mCPBA (10) $CHCl_3$, rt, 24 h	0[c]	–
2	mCPBA (10) Na_2CO_3 $CHCl_3$, rt, 24 h	26	19
3	TBHP (20) Na_2CO_3, ^{t}BuOH, rt, 24 h	0[c]	–
4	H_2O_2 (10) Na_2CO_3, EtOAc, rt, 24 h	4.4	49
5	TBHP (20), $VO(acac)_2$ (5 mol %) Na_2CO_3, ^{t}BuOH, rt, 24 h	22	53[d]
6	DMDO (10) Na_2CO_3, CH_2Cl_2–H_2O, rt, 12 h	98	49
7	DMDO (10) Na_2CO_3, CH_2Cl_2–H_2O, −78 °C, 12 h	99	79

[a] [Substrates] = 0.1 mM (see SI, Scheme S2). Dimethyldioxirane (DMDO) was generated in situ by the oxidation of acetone with oxone.
[b] The de value was determined by chiral HPLC.
[c] Protonated **1a** was recovered.
[d] Inverse stereochemistry at the nitrogen was confirmed.

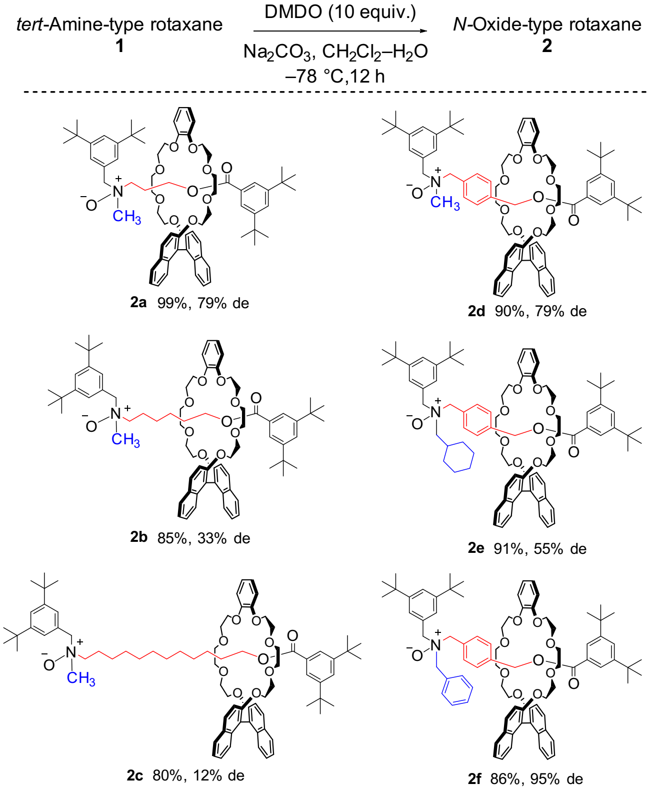
The diastereoselectivity was evaluated by chiral HPLC. The oxidation of **1a** with DMDO which gave the best chemical yield resulted in the formation of optically active **2a** with 49% de (entry 6). Fortunately, the de highly increased up to 79% by employing the reaction at −78 °C (entry 7). Meanwhile, $VO(acac)_2$-catalyzed oxidation inverted the stereochemistry of the nitrogen center. Although the stereoselection mechanism is not clear at present time, we may presume that an attractive interaction between the crown ether and $VO(acac)_2$ regulates the through-space chirality transfer from the wheel component as seen in the enhanced Cotton effect in CD spectrum (SI, Fig. S24).

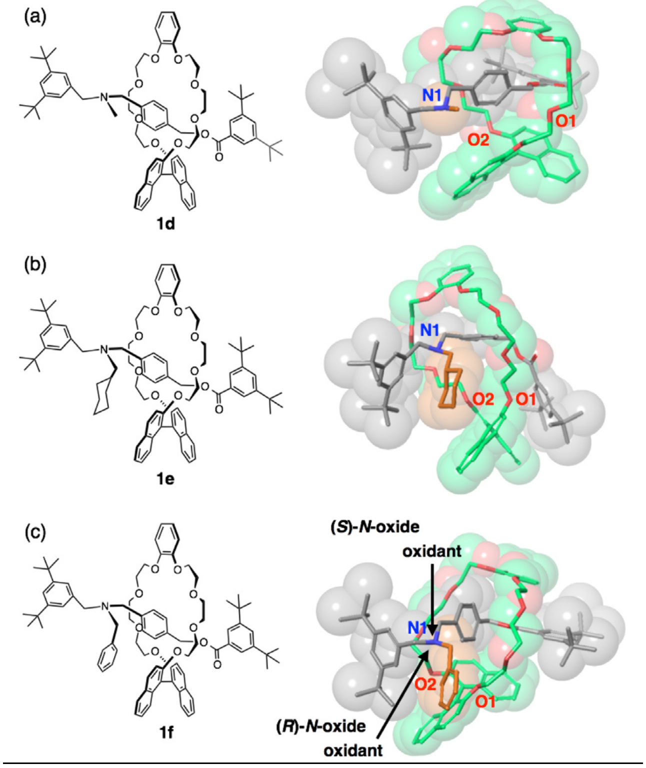
The structure effect of the rotaxane substrate on the yield and the de of the amine *N*-oxide was studied with the structure-different rotaxanes prepared in Scheme 1. Under the optimized conditions (DMDO, sodium carbonate, dichloromethane–water, −78 °C, 12 h), all rotaxanes underwent the oxidation to give the corresponding amine *N*-oxides in high chemical yields (80–99%) (Table 2). Meanwhile, the de clearly depended on the rotaxane's structure as discussed below.

The effect of the alkylene chain length of the axle component, or the distance of the reaction center from the chiral crown ether wheel, was investigated with **1a**–**1c**. As the chain length increased, the de value of **2a**–**2c** clearly dropped, as expected, while the chemical yield did not change. Since the crown ether wheel statistically localizes around the ester group due to the weak CH—O hydrogen bonding with the α-proton to the ether oxygen, the results can be reasonably explained.

The introduction of a *p*-phenylene moiety into the axle component (**1d**) caused the great enhancement of the de value (**2d**, 79%, Table 2) in comparison with that of **2b** (33%, Table 2), although the chemical yield was equally high. Since the length of the axle component is similar, the remarkable increase would come from the rigidity or the occupation of the wheel cavity, which makes effective through-space chirality transfer in the case of **1d**, i.e., (i) the

Table 2
Synthesis of rotaxane amine *N*-oxides **2** by the oxidation





rotaxane	yield /%	de /%	d1(N–**O1**) /Å	d2(N–**O2**) /Å	Δ|d1-d2| /Å
1d	90	79	5.94	6.97	1.03
1e	91	55	6.58	6.31	0.27
1f	86	95	4.96	5.86	0.90

Calculated structures of **1d**, **1e**, and **1f** were optimized at OPLS2005 force field level by MacroModel.

Figure 1. Calculated structures of **1d**, **1e**, and **1f**.

interconversion of nitrogen center in **1d** is presumably slower than that in **1b** by the effect of the rigid and heavy substituent so as to fix the chirality of nitrogen center, (ii) the rigid conformation enables the efficient through-space transfer of structural information by limiting the conformation. Another explanation can be obtained from Hirose's report where the mobility of the wheel component along the axle component is higher with the rigid axle rather than the flexible one because of the fixed conformation reduces the steric barrier for the mobility.[14] Namely, rigid conformation of rotaxane may affect the efficiency of the through-space chirality transfer.

Furthermore, the effect of *N*-substituent on the axle component was also investigated with **2d**–**2f** (Table 2). The oxidation of **1d**–**1f** proceeded efficiently to give high yields over 80% of the corresponding amine *N*-oxides (**2d**–**2f**). The lower yield of **2d**–**2f** would be the steric hindrance of the rigid structures comparing to **1a**. The most striking result is the very high de for **1f** (95% de) in comparison with those of **1d** (79% de) and **1e** (55% de). Thus, we could synthesize optically active rotaxane amine *N*-oxide with excellent de in a high yield. However, it is rather difficult to explain the reason for such a high diastereoselectivity in the simple *N*-oxidation of a *tert*-amine having *N*-benzyl group with DMDO without any catalyst, we suggest the intervention of some special interaction between the benzyl group and the chiral wheel component.

To evaluate the effect on the *N*-substituent, we compared the optimized structures of **1d**–**1f** (generated by Macromodel with OPLS2005 force field, Fig. 1), because we could obtain no single crystal suitable to X-ray analysis in all amine- and amine *N*-oxide rotaxanes.

Distances between the nitrogen center on the axle and the oxygen atoms of the crown ether wheel neighboring the binaphthyl unit (O1 and O2) in the optimized structures were calculated as the distance from the chiral center (d1 and d2), and are summarized in Figure 1. From the distances in **1e** which gave the lowest diastereoselectivity (Table 2), both d1 and d2 are larger than those of **1d** and **1f**. Furthermore, the difference between d1 and d2 is smaller than that of **1d** and **1f**. Therefore, the chiral wheel component is kept away from the nitrogen moiety due to the bulkiness of cyclohexyl group in **1e**. The results of Table 2 and Figure 1 reveal that both the oxidation and the through-space chirality transfer are kinetically controlled in **1e**.

On the other hand, the shorter distances d1 and d2 in **1f** coincides with the highest de. The d1 and d2 distances of **1f** much shorter than those of **1d** must require other reason than the bulkiness of the *N*-substituent, because benzyl group (**1f**) is obviously bulkier than methyl group (**1d**). At present time, we believe that the π–π interaction between the benzyl group and the binaphthyl group makes them nearer. As a result, the chirality transfer worked much effectively in **1f** among them, giving the 95% de. Since we could not directly determine the stereochemistry of the major products, the main stereochemistry of the nitrogen center was assumed by the stereospecificity derived from the optimized structures. The optimized structures for **1d**–**1f** took '*S*' configuration for the nitrogen center (Fig. 1), and thereby the product amine *N*-oxide should take *R*-configuration when the oxidant approaches to the O2 atom side. To generate (*S*)-*N*-oxide, the reaction should pass the interconversion of nitrogen central chirality followed by the rearrangement of the components. This is kinetically disadvantageous process compared to the process for generation of (*R*)-*N*-oxide. The improvement of de at lower temperature as seen in entries 6 and 7 (Table 1) obviously supports that this reaction proceeded under the kinetic control. Additional calculation of both (*S*)- and (*R*)-amine *N*-oxides (**2f**) indicated (*R*)-conformer takes a similar conformation to **1f** rather than (*S*)-conformer, suggesting the preferential formation of the rotaxane amine *N*-oxide with (*R*)-configuration at the nitrogen center in thermodynamic (SI, Figs. S1 and S2).

Conclusion

In conclusion, we have succeeded in synthesizing optically active rotaxane amine *N*-oxides in up to 95% diastereomeric excess and up to 99% yield via the oxidation of the *tert*-amine moiety of the axle component of the rotaxanes having a chiral crown ether wheel via the effective through-space chirality transfer. From the structural effect of the rotaxanes, it was concluded that not only the distance between the reaction center and the chiral center but also the axle rigidity as well as the presence of some interactions between the components promote the efficient through-space chirality transfer. We expect that this optically active rotaxane amine *N*-oxides can be utilized as the unique chiral sources.

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Supplementary data

Supplementary data (experimental procedures, spectra and structural calculation data) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2016.08.046.

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