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Asymmetric Benzoin Condensation Catalyzed by Chiral Rotaxanes Tethering a Thiazolium Salt Moiety via the Cooperation of the Component: Can Rotaxane Be an Effective Reaction Field?

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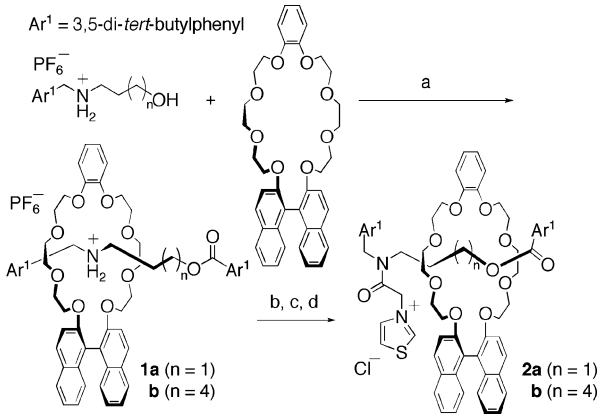
Although the chemical field formed by rotaxane components can provide a unique field based on noncovalent bonding, the chemical functions of rotaxanes[1] have rarely been explored. Vögtle et al. reported the reduced reactivity of the axle component controlled by the wheel in an amide-based rotaxane.[2] Also, Rowan et al. recently achieved the epoxidation of the axle by using the wheel component as catalyst.[3] These results showed the first intramolecular rotaxane catalyst mimicking the DNA enzyme λ-exonuclease.[4] We previously showed an unexpectedly lowered acidity of the ammonium moiety on the axle[5a] and achieved the isolation of a reactive intermediate placed on the axle,[5b] where in both cases the axle is effectively surrounded by the crown ether wheel. Further, the asymmetric radical hydrogen abstraction of the axle under the influence of the chiral crown ether wheel has also been reported.[6] The rotaxane field made by mechanically linked wheel and axle components may give an unprecedented space for recognition and reaction. We focused on the chiral rotaxane field for catalytic asymmetric reaction to evaluate the potentiality of the rotaxane field. The chiral environment of a rotaxane-based catalyst system is characterized by cooperation between the axle and the wheel. We chose benzoin condensation for the evaluation of the rotaxane field, which is catalyzed by thiazolium salts.[7] Although the asymmetric benzoin condensation catalyzed by artificial chiral thiazolium salts has not yet achieved high asymmetric yields,[8] the enzymatic asymmetric reaction field that surrounds the thiazolium salt moiety is highly enantioselective.[9] If the chiral wheel component surrounds the thiazolium salt moiety laid on the axle, the rotaxane field may be regarded as an enzyme-like asymmetric reaction field. Also of interest is the asymmetric induction that occurs from the chiral point on the axle. In this paper, we wish to report the first intermolecular chiral rotaxane catalyst, that is, the asymmetric benzoin condensation catalyzed by optically active rotaxanes.

First, chiral rotaxane catalyst **2** was designed to realize the through-space chirality transfer from the wheel. Scheme 1 shows the synthesis of **2** from an optically active crown ether. According to the tributylphosphine-catalyzed acylative end-capping protocol,[10] chiral rotaxane **1** was synthesized (yield: 20% for **1a**, and 71% for **1b**). After the acylation of **1** with chloroacetic anhydride (yield: 88% for **2a**, and 92% for **2b**), treatment with thiazole followed by anion exchange afforded the chiral thiazolium salt **2** (yield: **2a** 52%, and **2b** 64%). The structures of **1** and **2** were determined by ^{1}H NMR, IR, and FAB-MS spectra, and their optical rotatory power was assessed.

The benzoin condensation of benzaldehyde (1.8 M) catalyzed by **2a** (0.18 M) in the presence of triethylamine (0.18 M) in methanol was carried out for 24 h at 0 °C. The product benzoin **4a**

Scheme 1 [a]



[a] Conditions: (a) 3,5-di-*tert*-butylbenzoic anhydride, Bu_3P, CH_2Cl_2, room temperature, 3 h, 20% for **1a** and 71% for **1b**. (b) $(ClCH_2CO)_2O$, Et_3N, DMF, 50 °C, 24 h, 88% for **1a** and 92% for **1b**. (c) thiazole, NaI, 80 °C for **1a** and room temperature for **1b**, 24 h. (d) Amberlite IRA-400 (Cl type), 52% for **2a** and 64% for **2b** in two steps.

was isolated in an excellent yield (90%) by chromatographic purification. Although the asymmetric yield of **4a** (21%ee) was not very high (run 1), the ee of **4a** increased up to 32% (run 2) when 0.018 M of **2a** was used. The ee value of the products as determined by HPLC with a chiral column was independent of the length of the reaction period (3−24 h). The results suggest the good catalytic ability of **2a**, whereas the dependency of the ee value on the catalyst concentration may be indicative of the presence of two possible catalytic pathways including a stereoselection via nonsingle molecular catalysis.[11]

The condensations at certain concentrations (0.004 M catalyst and 0.8 M substrate) were examined to characterize and compare the rotaxane catalysts. The results are summarized in Table 1. Inspection of the data of Table 1 (runs 1−8) revealed the through-space chirality transfer between the wheel and axle components of **2a** in terms of the formation of an optically active product. Table 1 data also show that (i) the length of the axle component slightly affects the chemical and asymmetric yields (runs 9−11), (ii) the introduction of substituents (Me (**3b**) and Cl (**3c**)) on benzaldehydes decreases the chemical reactivity (runs 4, 7, and 8), (iii) dimethyl sulfoxide as solvent causes an increase in chemical yield and a decrease in asymmetric yield, although the degree of both yields is small (run 6), and (iv) a typical temperature effect characterized by a decrease in chemical yield and an increase in optical yield occurs as the temperature is lowered (runs 3−5).

The molecular model studies of **2** showed that the rotation of the wheel is not free and that the binaphthyl group tends to access the thiazolium moiety to avoid the steric repulsion against the

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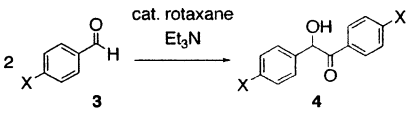
Table 1. Asymmetric Benzoin Condensation with Chiral Rotaxane Catalysts **2**,[12] **5**, and **6**[a]

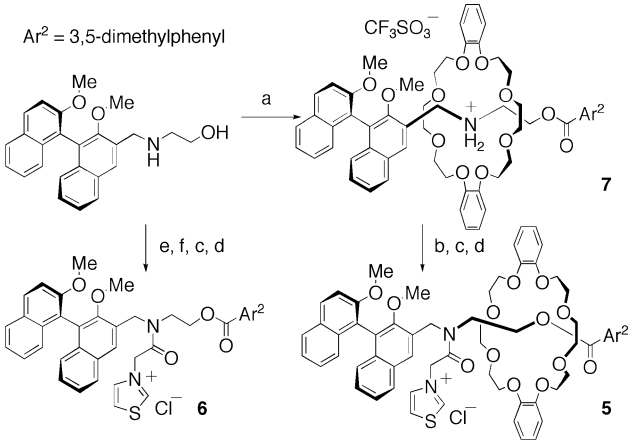


3, 4	X
a	H
b	CH_3
c	Cl

run	catalyst (mol %)	aldehyde (M)	solvent	temp/°C	yield/%	ee/%[b]
1	**2a** (10)	**3a** (1.6)	CH_3OH	0	90	21 (*R*)
2	**2a** (1)	**3a** (1.6)	CH_3OH	0	14	32 (*R*)
3	**2a** (5)	**3a** (0.8)	CH_3OH	−20	17	27 (*R*)
4	**2a** (5)	**3a** (0.8)	CH_3OH	0	34	23 (*R*)
5	**2a** (5)	**3a** (0.8)	CH_3OH	30	70	16 (*R*)
6	**2a** (5)	**3a** (0.8)	DMSO	30	79	11 (*R*)
7	**2a** (5)	**3b** (0.8)	CH_3OH	0	10	25 (*R*)
8	**2a** (5)	**3c** (0.8)	CH_3OH	0	16	18 (*R*)
9	**2b** (5)	**3a** (0.8)	CH_3OH	0	34	16 (*R*)
10	**2b** (5)	**3b** (0.8)	CH_3OH	0	10	21 (*R*)
11	**2b** (5)	**3c** (0.8)	CH_3OH	0	28	11 (*R*)
12	**5** (5)	**3a** (0.8)	CH_3OH	−20	7	24 (*S*)
13	**5** (5)	**3a** (0.8)	CH_3OH	0	40	19 (*S*)
14	**5** (5)	**3a** (0.8)	CH_3OH	30	82	8 (*S*)
15	**5** (5)	**3b** (0.8)	CH_3OH	0	10	25 (*S*)
16	**5** (5)	**3c** (0.8)	CH_3OH	0	22	13 (*S*)
17	**6** (5)	**3a** (0.8)	CH_3OH	−20	56	3 (*S*)

[a] All reactions were carried out in the presence of **2** and 0.16 M triethylamine for 24 h. [b] Determined by chiral HPLC (DAICEL CHIRALPAK AD-H).

Scheme 2 [a]



[a] Conditions: (a) DB24C8, 3,5-dimethylbenzoic anhydride, Ti(*i*-PrO)$_4$, TfOH, CH_2Cl_2, room temperature, 6 h, 75%. (b) $(ClCH_2CO)_2O$, Et_3N, DMF, 50 °C, 24 h, 94%. (c) thiazole, NaI, 80 °C, 24 h. (d) Amberlite IRA-400 (Cl type), 50% for **5** and 99% for **6** in two steps. (e) $(ClCH_2CO)_2O$, THF, −40 °C, 15 h, 87%. (f) 3,5-dimethylbenzoic anhydride, Bu_3P, CH_2Cl_2, room temperature, 11 h, 79%.

terminal bulky 3,5-di-*tert*-buthylphenyl groups of the axle. The stereoselectivity confirmed in this condensation might come from the strong influence of the crown wheel that surrounds the thiazolium moiety.

Because a through-space chirality transfer was observed with **2**, a new rotaxane catalyst **5** was designed to evaluate the through-bond chirality transfer. The synthesis of this thiazolium salt moiety-containing rotaxane **5** possessing a (*R*)-binaphthyl group at an axle terminal is shown in Scheme 2. The starting rotaxane **7** was obtained according to the triflic acid-catalyzed acylative end-capping method.[13] The synthesis of **5** was performed by a procedure similar to that employed for **2**. The corresponding reference compound **6** without wheel component was also prepared.

As shown in Table 1, the chirality transfer through bond was also confirmed with **5** under the same conditions, although the ee values of **4** were a little lower than those of **2** (runs 3−5, 7, 8, and 12−16). The much lower ee value of **4** with the wheel-free catalyst **6** (run 17) clearly reveals the presence of a wheel component in the stereoselection step. The role of the wheel component linked mechanically to the reaction center can be understood as one of protection of the less stereoselective side of the asymmetric field or as one of enhancement of the influence of the chiral environment.

In summary, our first attempt to demonstrate the catalysis of rotaxanes in this paper may help clarify the fundamental features of the rotaxane structure which was shown to give a unique reaction field in asymmetric benzoin condensation. A more precise design for the asymmetric rotaxane catalyst based on the guiding principle obtained here will result in rotaxanes with higher chemical and asymmetric yields.

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Supporting Information Available: Experimental procedures and spectroscopic data of the catalysts (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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