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# Regiodivergent Desymmetrization Reaction of *meso*-Azabicycloheptene Providing Two Enantioenriched Structural Isomers

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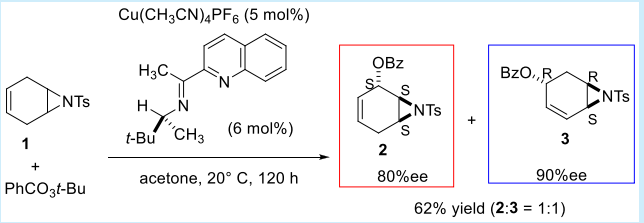
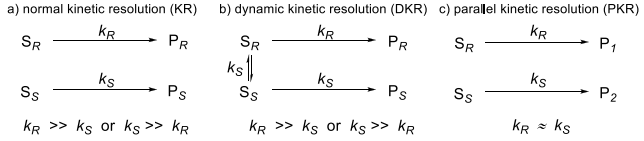
**ABSTRACT:** A novel catalytic asymmetric reaction is reported where the regiodivergent desymmetrisation of *meso*-azabicycloheptene via allylic oxidation using a single chiral copper catalyst produced two different, enantioenriched structural isomers in high optical purity starting from a single compound. The enantioselectivity of the two structurally isomeric compounds was enriched to >99.5% ee after derivatization.





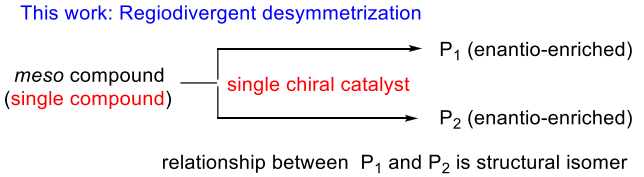

Catalytic asymmetric reactions are widely applicable, easily reproducible, and economically feasible. Alongside the development of chiral catalysts, discovering new phenomena regarding these reactions is also desirable.[1] Herein, we disclose new phenomena relating to the asymmetric reaction, where two structural isomers were obtained from a single starting material using a single chiral catalyst with high enantioselectivity. In asymmetric reactions the product is an enantiomer of one compound, except for those obtained via parallel kinetic resolution (PKR). Kinetic resolution can be classified into three modes, one of which being PKR (Scheme 1).

**Scheme 1. Classification of Kinetic Resolution: (a) Normal Kinetic Resolution (KR); (b) Dynamic Kinetic Resolution (DKR); (c) Parallel Kinetic Resolution (PKR)**




In PKR,[2] a single catalyst gives two products from a racemic mixture. When the products are not isomers but compounds with different structures, this reaction is called chemodivergent PKR.[3] Furthermore, regiodivergent PKR uses a single catalyst to afford regioisomeric products from racemic compounds,[4−7] and stereodivergent PKR reactions transform racemic compounds into diastereomeric isomers.[8] In this letter, we report the first example of a novel asymmetric reaction in which a single catalyst was employed to give two, enantioenriched, structural isomers with high enantioselectivity from a single substrate. This reaction appears to be similar to PKR; however, kinetic resolution reactions use racemic compounds (i.e., enantiomeric mixtures) as the starting material, while the present method employs a single *meso* compound (Scheme 2).

**Scheme 2. Regiodivergent Desymmetrization**




The oxidation of allylic alkenes by a peroxy ester and copper catalyst is called Kharasch−Sosnovsky reaction.[9] The enantiotopic relationship between the allylic protons of cycloalkenes, such as cycloheptene and cyclohexene, suggests that enantioselective Kharasch−Sosnovsky reactions could be possible,[10−13] which we reported an example of such a reaction.[14] In addition, a single reaction using *meso*-4,5-epoxyhex-1-ene as the substrate constructed three stereocenters.[15] During the course of this study, we found that reacting 7-tosyl-7-azabicyclo[4.1.0]hept-3-ene (**1**) with *tert*-butyl-perbenzoate in the presence of 5 mol % Cu(CH$_3$CN)$_4$PF$_6$ and 6 mol % (*R*,*E*)-*N*-(3,3-dimethylbutan-2-

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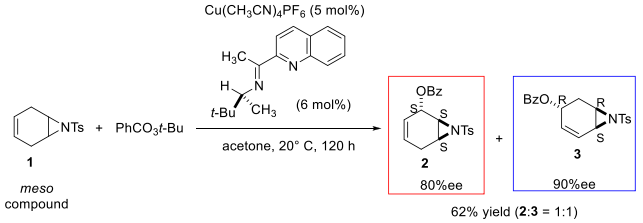
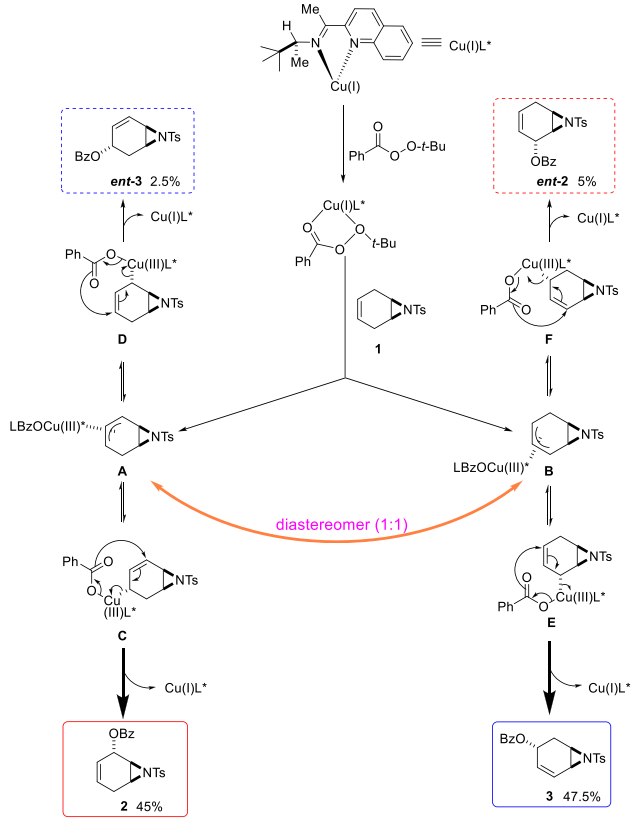
yl)-1-(quinolin-2-yl)ethan-1-imine afforded a 1:1 mixture of (1*R*,2*R*,6*R*)-7-tosyl-7-azabicyclo[4.1.0]hept-3-en-2-yl benzoate (**2**) and (1*R*,3*R*,6*S*)-7-tosyl-7-azabicyclo[4.1.0]hept-4-en-3-yl benzoate (**3**) in 80% ee and 90% ee, respectively, in an overall yield of 62% (Scheme 3). The absolute configuration was determined by X-ray crystal structure analysis.[16]

**Scheme 3. Reacting *meso*-Aziridine 1 with *tert*-Butyl-Perbenzoate in the Presence of a Chiral Cu Catalyst**



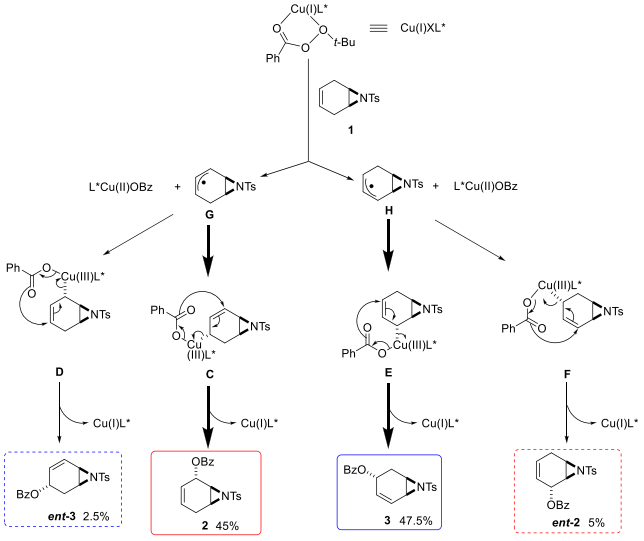

Several species and reaction paths were proposed and have been reported for copper-catalyzed Kharasch−Sosnovsky-type allylic oxidations, including the Beckwith−Zavitsasa mechanism,[17] the Slough mechanism,[18] and Salvatella's theoretical mechanism.[19] For the present asymmetric reaction, we propose two plausible pathways (Scheme 4 and Scheme 5). The first

**Scheme 4. Proposed Reaction Pathway**




proposed pathway (Scheme 4) begins with the chiral catalyst species Cu(I)L*,which is composed of a chiral *N*,*N*-bidentate ligand and a Cu(I) precursor. As for the role of the used chiral ligand on copper, after screening of a variety of similar *N*,*N*-bidentate we developed,[14] the used *N*,*N*-bidentate ligand having the bulky *tert*-butyl afforded the highest enantioselectivity for the formation of compounds **2** and **3**. The use of the ligand having ethyl or phenyl instead of *tert*-butyl afforded a lower chemical yield and enantioselectivity (ethyl: 46% yields, 36% ee of **2** and 54% ee of **3**; phenyl: 54% yields, 66% ee of **2** and 44% ee of **3**). This Cu(I)L* complex reacts with *tert*-butyl perbenzoate to form peroxide complex Cu(I)XL*, which subsequently reacts with **1** to afford diastereomeric Cu(III)-$\pi$-allyl intermediates **A** and **B** in a 1:1 ratio. From diastereomeric intermediate **A**, there are two regioselective routes that form $\sigma$-allyl-Cu(III) complexes **C** and **D**, the formation of **C** being preferred. Similarly, from intermediate **B**, two regioselective routes will form $\sigma$-allyl-Cu(III) complexes **E** and **F**, in which **E** formation is preferred. In both cases each set of complexes (**C** and **D**; **E** and **F**) will be in equilibrium. The origin of the preferences for **C** and **E** is complicated and is detailed in the Supporting Information. Attack by the benzoate carbonyl oxygen to the bottom face (opposite side to the aziridine moiety) of **C** affords compound **2** in 45% yield. On the other hand, in a less regioselective manner, similar carbonyl oxygen attack of **D** afforded *ent*-**3** in 2.5% yield. From intermediate **B**, allyl $\sigma$-Cu(III) complex **E** was formed regioselectively to afford **3** in a 47.5% yield. The regiomer minor complex **F** gave *ent*-**2** in 5% yield. As for the role of the chiral ligand on copper, the bulky *tert*-butyl moiety in the *N*,*N*-bidentate ligand is essential for the formation of compounds **2** (vs *ent*-**3** from intermediate **A** to **C** vs **D**) and **3** (vs *ent*-**2** from intermediate **B** to **E** vs **F**) predominantly in high enantioselectivity. The steric effect of the *tert*-butyl group was depicted in Scheme S1 (Supporting Information). Compounds **2** and **3** are structural isomers; therefore, we named this phenomenon 'regiodivergent desymmetrization'. The unique feature of this reaction is that two structural isomers were formed with high enantioselectivity from a single compound using a single catalyst.

**Scheme 5. An Alternative Proposed Reaction Mechanism**




An alternative reaction mechanism (Scheme 5) was proposed in which the reaction of the Cu(I)XL* complex with **1** regioselectively gives the $\sigma$-allyl-Cu(III) complexes **C** and **D** via $\pi$-allyl radical **G**. Compound **2** was obtained in 45% yield from **C** by a regio- and stereospecific oxygen attack, and *ent*-**3** was obtained in 2.5% yield from **D** through the same process. $\sigma$-Allyl-Cu(III) complexes **E** and **F** could also be formed via $\pi$-allyl radical **H**, where **3** (the structural isomer of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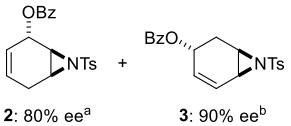
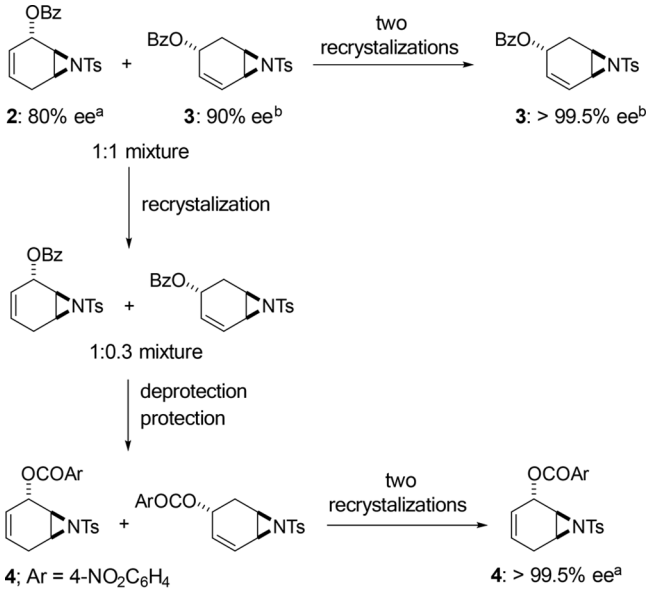
2) was obtained in 47.5% yield from **E**, and *ent*-**2** was obtained in 2.5% yield from **F**.

We then carried out the separation of **2** and **3** and enriched the optical purity as follows. The separation of **2** and its structural isomer **3** was achieved by preparative high-performance liquid chromatography (PHPLC). Compound **2** (80% ee) was recrystallized from the 1:4 mixture to afford **2** with an improved ee of 97%.

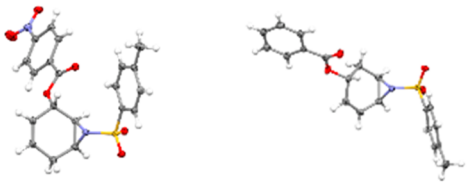



The ee of compound **3** (90% ee) was also increased to >99.5% ee by recrystallization from toluene/hexane (1:2) or from ethyl acetate/hexane (1:4). An alternative procedure without the use of PHPLC is shown in Scheme 6. Two, direct

**Scheme 6. Increasing Optical Purity of the Aziridines**




[a] Determined by chiral HPLC analysis (CHIRALCEL OD-H).
[b] Determined by chiral HPLC analysis (CHIRALCEL OJ-H).

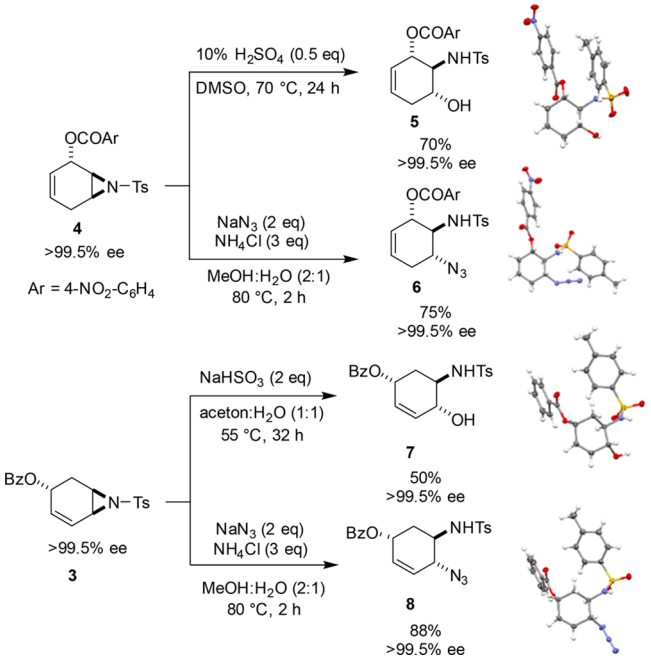


**4** (*p*-$NO_2$ derivative of **2**) **3**

recrystallizations of the 1:1 mixture of **2** and **3** gave >99.5% ee of **3**. The benzoyl group in the residual product mixture (1:0.3) was deprotected and then protected as its 4-nitrobenzoate, and two successive recrystallizations afforded >99.5% ee of **4**.

To obtain useful chiral building blocks, we carried out aziridine ring opening of compounds **4** and **3** by $H_2O$ and $NaN_3$. The reaction took place in both a regio- and stereoselective manner to afford optically pure chiral building blocks 5, 6, 7, and 8 in >99.5% ee (Scheme 7). It should be

**Scheme 7. Ring Opening Reactions of Aziridines to Give Chiral Building Blocks**




noted that in the case of compound **3** ring opening of aziridine occurred regioselectively next to the carbon of the double bond. These chiral building blocks are useful intermediates for synthesizing (−)-oseltamivir phosphate (Tamiflu)[20] and its derivatives. Furthermore, after ozonolysis, a variety of acyclic natural[21] and unnatural products can be synthesized using these chiral building blocks.[22]

In conclusion, the first example is reported of an asymmetric reaction in which two structural isomers with high enantioselectivity from a single compound using a single chiral catalyst was developed. Our findings demonstrate further utility of *meso* compounds in catalytic asymmetric reactions.

## ■ ASSOCIATED CONTENT

### Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00036.

Classification of kinetic resolution; Additional consideration of reaction mechanism; General Information Procedure for synthesis of 7-tosyl-7-azabicyclo[4.1.0]-hept-3-ene (**1**) and characterization of compound **1**; Typical procedure for asymmetric allylic oxidation of 7-tosyl-7-azabicyclo[4.1.0]hept-3-ene (**1**) and characterization of compounds **2** and **3**; Characterization of compounds **4**−**8** and procedure and characterization of compound **5**−**8**; HPLC charts of compounds **2**−**4**; $^1H$ and $^{13}C\{^1H\}$ spectra of compounds **1**−**8**; Crystallographic details of compounds **3**−**8** (PDF)

### Accession Codes

CCDC 2032340−2032345 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.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### Notes

The authors declare no competing financial interest.

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