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Copper-Catalyzed Desymmetrization of *N*-Sulfonylaziridines with Methylmagnesium Halides

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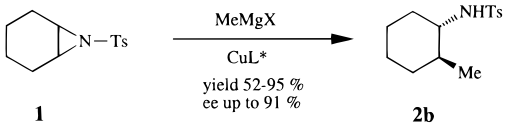
ABSTRACT



Cyclohexene *N*-*p*-toluenesulfonylimine (1) undergoes enantioselective ring opening to 2b upon treatment with methylmagnesium halides or MeLi in the presence of chiral Cu-catalysts. No activation of the aziridine by Lewis acid is required. Enantioselectivities of up to 91% have been observed under optimized conditions with the chiral imine ligand derived from phenylalanine. The same system reacts with cyclohexene oxide to afford *trans*-2-methylcyclohexanol with 50% yield and 10% ee.

The desymmetrization of *meso*-epoxides[1] may be effected via enantioselective β-deprotonation to afford allylic alcohols,[2] α-deprotonation to furnish carbenes and their subsequent products of intramolecular insertion,[3] and nucleophilic ring opening under stoichiometric[4] and catalytic conditions.[5] The reaction of cyclohexene oxide with organometallic reagents has been reported by several groups. Epoxide opening with organolithium reagents requires activation by a Lewis acid. Enantioselectivities of up to 47% have been observed with BF_3 and chiral ethers as external ligands.[6] Sparteine was found even more efficient in epoxide opening with organolithium reagents and produced enantioselectivities of up to 87% in selected cases.[7] Opening of epoxides by organocopper reagents proceeds without activation by Lewis acids. However, enantioselectivities reported for opening of cyclohexene oxide with organocuprates in the presence of chiral ligands are disappointing.[8] In contrast, only a few procedures for ring opening of aziridines are known. The reaction usually requires strong nucleophiles. Opening of aziridines has been reported with catalytic amounts of lanthanides, in particular Yb(III).[9] Organocuprates reportedly open N-activated aziridines with high yield and high regio- and stereoselectivity.[10,11]

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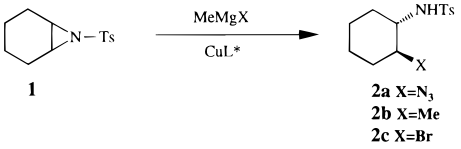
In the context of our research on asymmetric aziridinations of olefins, we observed that some *N*-sulfonated aziridines underwent ring opening in the presence of electrophiles under mild conditions.[12] We have now explored this observation with the objective of developing a catalytic protocol for desymmetrization of *meso*-aziridines.

Exploratory experiments with cyclohexene *N*-*p*-toluenesulfonyl imine (**1**) revealed only limited reactivity toward Lewis acid-catalyzed ring opening. Typically, reaction of **1** with NaN_3 went to completion in refluxing acetonitrile within 24 h and aforded **2a**[13] in 85% yield (Scheme 1).

Scheme 1



$TMSN_3$ in CH_3CN at reflux, in turn, even in the presence of Cu(II)- or Zn(II)-catalysts afforded **2a** in 58−81% yield after up to 12 h. No reaction occurred with $TMSN_3$ in conjunction with Jacobsen's [Cr(salen)] catalyst, which is known to exhibit exceptional reactivity and selectivity in opening of epoxides.[5d,e] The aziridine **1** reacted when exposed to MeMgBr in THF (0 °C, 6 h), but the resulting product was not the expected *trans*-methyl-*N*-*p*-toluenesulfonylcyclohexanamine (**2b**), but rather the *trans*-2-bromo derivative **2c**,[14] which was isolated in 91% yield. However, when the reaction was carried out in the presence of 10% of [Cu(acac)$_2$], ring opening occurred readily (0 °C, 1 h) and **2b**[15] was formed in 85% yield.

Next, a series of known Cu-catalysts was tested in this process. Reactions were carried out by adding the organometallic reagent (1.0 equiv) in THF at 0 °C to a THF solution containing the aziridine **1** and the catalyst with a 10:1 substrate/catalyst ratio. The catalysts **5**, **6**, and **7** were prepared in situ, by addition of 2 equiv of the ligand of interest to [Cu(OTf)$_2$], and **4** by analogy with CuI. In the case of **3** and **8a**−**8e** the Cu-complexes were synthesized and isolated according to literature procedures. In general, yields for aziridine opening varied in the range of 60−89%, and competing halide attack on **1** was the principal cause for low yields of **2b**.

Poor enantioselectivity for opening of **1** was observed with a Cu-semicorrin catalyst (0%),[16] a salicylaldehyde-derived Schiff base complex,[17] and a Schiff base complex derived from 1,2-diaminocyclohexane.[5d,e] The Cu-pybox catalyst[18] was equally ineffective (6% ee). The results with the more successful catalysts are summarized in Table 1.

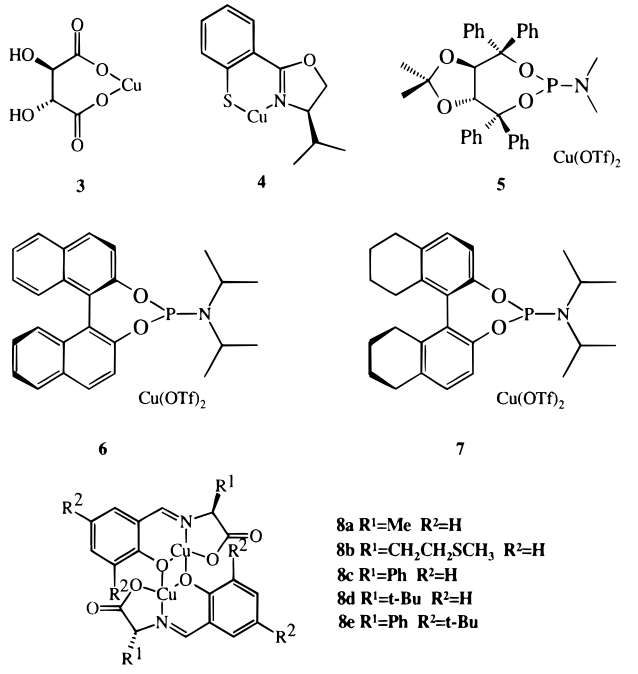


Figure 1. Chiral Cu-catalysts.

Table 1. Ring Opening of Aziridine **1** to **2b** with MeMgBr[a]

catalyst	time, h	yield, %	ee, %[b]	abs conf
[Cu(acac$_2$]	1.0	85		
3	3.0	70	30	1*S*, 2*S*
4	2.5	30	51	1*S*, 2*S*
5	2.0	84	29	1*S*, 2*S*
6	2.5	60	56	1*S*, 2*S*
7	2.0	80	32	1*S*, 2*S*
8c	2.0	89	55	1*S*, 2*S*
8d	2.0	71	39	1*S*, 2*S*
8e	2.0	80	32	1*S*, 2*S*

[a] Conditions: MeMgBr in THF/toluene added dropwise to **1** and catalyst in THF at 0°.[22] [b] Determined by HPLC (OD,H column with hexane/2-propanol, 9:1).

Inspection of Table 1 reveals no clear-cut relationship between catalyst structure and catalyst efficiency. The highest enantioselectivity resulted with the BINOL-derived amidites

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(15) Data of **2b**: ^{1}H NMR ($CDCl_3$) 0.81(3H, d), 0.98−1.25 (5H, m); 1.57−1.58 (2H, m); 1.70−1.72 (2H, m); 2.41 (3H, s); 2.64−2.65 (1H, m); 4.71−4.82 (1H, m); 7.27 (2H, d, J = 8); 7.76 (2H, d, J = 8); ^{13}C NMR ($CDCl_3$) 19.05 (q), 21.5 (q); 25.3 (t); 25.4 (t); 34.4 (t); 34.5 (t); 38.3 (d); 59.1 (d); 126.9 (d); 129.5 (d); 138.7 (s); 142.9 (*s*); HR MS 267.12804 ($C_{14}H_{21}NO_2S^{\bullet+}$, calcd 267.12930).

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6[19] and **7**,[20] respectively, and with the Schiff base complexes **8c**−**8e**,[21] which are obtained upon condensation of salicylaldehyde with amino acids. Within this latter series of catalysts, structural variation of the amino acid component had a remarkable effect on the enantioselectivity. The alanine- and methionine-derived complexes **8a** and **8b** were essentially unselective, while those containing phenylglycine (**8c**) and *tert*-leucine (**8d**) afforded ee's of 55% and 40%. Introduction of *tert*-butyl groups into the salicylaldehyde moiety (i.e., **8e**) had, however, no beneficial effect.

Optimization of the reaction conditions was carried out with the D-phenylglycine-derived Schiff base catalyst **8c** (Table 2). The selectivity of **8c** was found dependent not only upon the solvent but also upon the metal ion of the reagent and its counterion. The tendencies are contradictory, and no systematic trend may be spotted. MeMgCl is the least efficient Grignard reagent. MeMgBr is superior to MeMgI in THF, but is less efficient in Et_2O. In THF the yield decreased with increasing the amount of catalyst from 2 to 30%. At still higher catalyst concentration bromide attack predominated. However, acceptable yields could be obtained when MeMgBr was added slowly (in 10 min) to the reaction mixture rather than dropwise in 5 min. Thus with 30% of catalyst **2b** was formed in 52% yield and with 91% ee, but with 40% of **8c** the yield of **2b** dropped to an insignificant amount. The decrease in yield upon increasing catalyst concentration may be due to the presence of electrophilic Cu(II) species, which might catalyze bromide attack. Addition of excess ligand to the reaction with 10% of catalyst in THF had no beneficial effect. A high enantioselectivity of 83% was also observed in Bu_2O with 10% of catalyst.

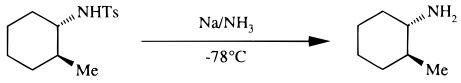
Table 2. Variation of Reaction Conditions for Ring Opening of **1** with **8c**[a]

reagent	cat,%	solvent	time, h	**2b**, yield, %	ee, %
MeMgCl	10	THF	2.0	75	20
MeMgBr	10	THF	2.0	89	55
MeMgI	10	THF	2.0	60	62
MeLi	10	THF	3.0	60	45
MeMgBr	2	THF	1.0	97	4
MeMgBr	5	THF	1.0	84	11
MeMgBr	20	THF	1.0	58	77
MeMgBr	30	THF	1.5[b]	52	91
MeMgCl	10	Et_2O	2.0	91	25
MeMgBr	10	Et_2O	2.0	70	70
MeMgI	10	Et_2O	2.0	20	61
MeLi	10	Et_2O	2.5	60	40
MeMgCl	10	Bu_2O	1.5	60	41
MeMgBr	10	Bu_2O	2.0	30	83
MeMgI	10	Bu_2O	2.0	0[a]	

[a] Conditions: see Table 1. [b] Addition of MeMgBr in 10 min.

The sulfonamide **2b** which resulted from reaction of **1** with **8d** was cleaved to the amine **9** (Scheme 2), which had $[\alpha]^{22}_D = +20.2$ ($c = 10$, ether). The absolute configuration of **(+)-9** ($[\alpha]^{19}_D = +30.8$) has been determined to be 1*S*,2*S*.[23] The absolute configurations assigned to the major enantiomers of the sulfonamides **2b** in Table 1 were assigned on the grounds of the HPLC retention times relative to those obtained with **8c**.

Scheme 2



2b **9**

Application of the procedure to other organometallic reagents is in progress. With PhMgBr the highest ee achieved so far was 30%.

The reaction conditions are in principle also applicable to ring opening of epoxides. Thus cyclohexene oxide reacted with MeMgBr in the presence of 10% of **8c** at −20 °C to *trans*-2-methylcyclohexanol in 50% yield and 10% ee.

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(22) **General Procedure for Ring Opening of 1.** To **8c** (28 mg, 0.08 mmol) and **1** (200 mg, 0.80 mmol) in THF (2.0 mL) at 0 °C was added MeMgBr in THF/toluene (0.6 mL, 0.8 mmol), dropwise. After stirring for 3 h at 0 °C the mixture was decomposed (NH_4Cl) and extracted with Et_2O. Purification of the crude product (column chromatography, SiO_2, hexane/AcOEt, 4:1) gave **2b** (180 mg, 89% as colorless needles, mp 98−100 °C).

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