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Asymmetric aziridination: a new entry to optically active non-*N*-protected aziridines

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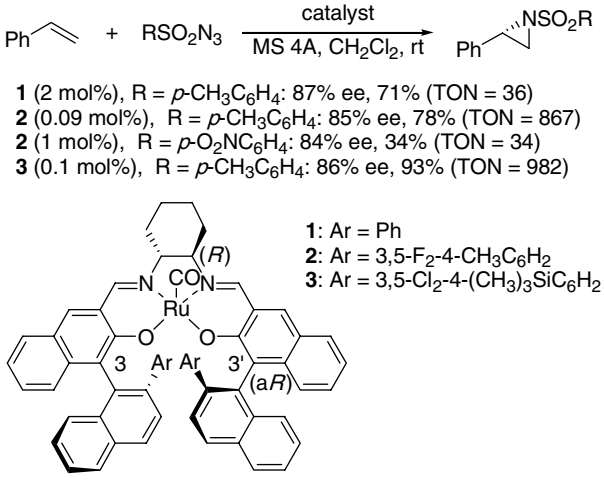
Abstract—A newly designed robust Ru(salen)(CO) complex **3** was found to catalyze asymmetric aziridination using azide compounds carrying *p*-nitrobenzenesulfonyl and 2-(trimethylsilyl)ethanesulfonyl (SES) groups, which are easily removable *N*-protecting groups under mild conditions, as a nitrene precursor in a highly enantioselective manner. In particular, the reactions with SES azide showed excellent enantioselectivity greater than 90% ee, except for one example.

Achievement of high selectivity and mild reaction conditions as well as realization of environmental benignity and high atom economy is a key issue in current chemical transformation. Since most organic compounds carry nitrogen functional group(s), C–N bond formation is a very important transformation for organic synthesis. Of many C–N bond formations, aziridination is extremely important, because aziridines, especially *N*-sulfonylated ones, undergo various nucleophilic ring-opening reactions due to their high reactivity and serve as potent synthetic intermediates for nitrogen-containing compounds.[1] Thus, much effort has been devoted toward the development of asymmetric aziridination with nitrene precursors possessing *N*-arylsulfonyl group and many highly enantioselective reactions have been reported to date.[2] However, most of them use *N*-arylsulfonyliminophenyliodinanes as the nitrene precursor and the atom economics and ecological benignity of those reactions remain at an unsatisfactory level, because a stoichiometric amount of iodobenzene was inevitably produced as the waste co-product.[3] Taking into consideration the above problems, aziridination using arylsulfonyl azides as precursor has been continuously studied, because it generates innocuous nitrogen as the only side product.[4] Although asymmetric aziridination using the azide compound in the presence of a copper or rhodium complex had also been reported, it needs UV irradiation to decompose the azide compound and it is modestly enantioselective.[5] We recently found that Ru(salen)(CO) complex **1** catalyzed asymmetric imidation of sulfides[6a,b] and aziridination[6c] using azide compounds without UV irradiation at room temperature in a highly enantioselective manner, but the turnover number (TON) of the catalyst in the aziridination of styrene was moderate (Scheme 1). The insufficient



Scheme 1.

Keywords: Ru(salen)(CO) complex; Asymmetric catalysis; Aziridination; Azide compound.
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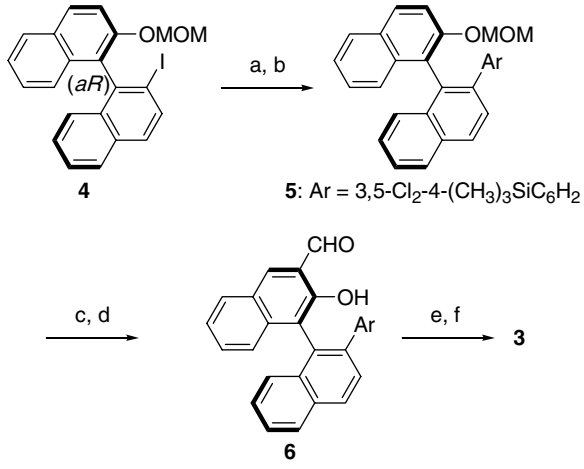
TON was attributed to an undesired intramolecular C–H insertion reaction of an intermediary azide–Ru species, in which the phenyl substituent of the C3- or C3′-naphthyl group was aminated to give a catalytically inactive species.[7] This knowledge prompted us to synthesize catalyst **2** that has a 3,5-difluoro-4-methylphenyl substituent instead of the phenyl substituent.[8] The TON of **2** in aziridination amounted to 867, when *p*-toluenesulfonyl azide (TsN_3) was used as the precursor. However, removal of the *N*-protecting simple arylsulfonyl group needs harsh conditions. This diminishes the utility of this aziridination. On the other hand, it has been reported that *N*-*p*-nitro- and *o*-nitro-benzenesulfonyl (*o*- and *p*-Ns)[9] and 2-(trimethylsilyl)ethanesulfonyl (SES)[10] groups can be removed under mild conditions. Complex **2** also catalyzed aziridination using *p*-nitrobenzenesulfonyl azide with high enantioselectivity, but



Scheme 2. Reagents and conditions: (a) $Pd(PPh_3)_4$ (5 mol %), 3,5-dichlorobenzeneboronic acid, toluene, 1 M Na_2CO_3, 100 °C, 92%; (b) *sec*-BuLi, THF, −78 °C, then $(CH_3)_3SiCl$, 64%; (c) *n*-BuLi, *N*,*N*,*N*′,*N*′-tetramethylethylenediamine, −78 °C, then DMF, 84%; (d) HCl/*i*-PrOH (20 w/w%), THF, 99%; (e) (1*R*,2*R*)-1,2-diaminocyclohexane sulfate, K_2CO_3, EtOH, 95%; (f) $Ru_3(CO)_{12}$, EtOH, reflux, 62%.

its TON was moderate (36) (Scheme 1). Though the mechanism of degradation of **2** was unclear, we speculated that the *o*-carbon or *p*-methyl group might be aminated. Therefore, we expected that a more robust catalyst could be constructed, if the two positions are somehow protected from the amination. Based on this idea, we attempted introducing a pentafluorophenyl group instead of the phenyl substituent. However, the desired complex could not be synthesized. Thus, we synthesized a new complex **3** that possessed a phenyl substituent bearing chloro and trimethylsilyl groups at its *m*- and *p*-positions, respectively. A bulky chloro substituent was expected to block its *o*-hydrogen atom more efficiently than the fluoro substituent. Aldehyde **6**, which was necessary for the synthesis of **3**, was prepared from (a*R*)-iodobinaphthyl **4** in four steps: (i) Suzuki–Miyaura coupling, (ii) trimethylsilylation, (iii) *o*-directed formylation, and (iv) deprotection (Scheme 2).[8] Condensation of **6** with (1*R*,2*R*)-1,2-cyclohexanediamine sulfate in the presence of K_2CO_3 and the treatment of the resulting salen ligand with $Ru_3(CO)_{12}$ in ethanol yielded complex **3**.

With **3** in hand, we first examined aziridination of styrene using TsN_3 at room temperature to evaluate its robustness (Scheme 1). The reaction proceeded with enantioselectivity of 86% ee similar to those obtained with **1** or **2** and the TON of **3** amounted to 982.

Encouraged by this result, we next examined aziridination of styrene with *p*-Ns azide in the presence of 0.1 mol % of complex **3**. To our delight, TON of **3** was found to be as large as 746 together with good enantioselectivity of 81% ee (Table 1, entry 1). The reaction with 1 mol % of **3** at 0 °C showed somewhat better enantioselectivity at the expense of TON, though it was still as high as 97 (entry 2). Aziridination of other terminal conjugated olefins also proceeded with high enantioselectivity (entries 3 and 4). However, the reaction of non-conjugated 1-octene was sluggish at 0 °C and slow even at elevated temperature, and the enantioselectivity was moderate (entry 5). We also examined aziridination

Table 1. Asymmetric aziridination of various olefins with *p*-NsN_3, *o*-NsN_3, or $SESN_3$ catalyzed by Ru(salen)(CO) **3**

Entry	Azide	Catalyst/mol %	R or substrate	Temp/°C	Time/h	Yield/%[a]	% ee[b]	TON[c]
1	*p*-NsN_3	0.1	Ph	rt	38	70	81	746
2	*p*-NsN_3	1	Ph	0	12	90	87	97
3	*p*-NsN_3	1	4-BrC_6H_4	0	12	93	83	94
4	*p*-NsN_3	1	PhC≡C—	0	12	98	98	99
5	*p*-NsN_3	2	1-Octene	Reflux	38	32[c]	56	16
6	*o*-NsN_3	0.1	Ph	rt	12	62	73	660
7	*o*-NsN_3	1	Ph	0	12	60	81	68
8	*o*-NsN_3	1	PhC≡C—	rt	12	58	87	59
9	$SESN_3$	0.1	Ph	rt	12	26	91	260
10	$SESN_3$	1	Ph	rt	12	100	90	—
11	$SESN_3$	1	Ph	0	12	99	92	99
12	$SESN_3$	1	4-BrC_6H_4	0	12	76	92	98
13	$SESN_3$	1	PhC≡C—	0	12	50	>99	51
14	$SESN_3$	5	1-Octene	Reflux	38	28[c]	77[d]	6
15	$SESN_3$	5	Indene	Reflux	38	47	98	26

[a] Isolated yield after silica gel chromatography, unless otherwise mentioned.
[b] Determined by HPLC analysis.
[c] Calculated according to ^1H NMR analysis.
[d] Determined by chiral HPLC analysis after the conversion into 2-naphthylsulfide derivative (Ref. 13).

with *o*-Ns azide. It was found that this azide was less reactive and the reaction with it was somewhat less selective than that with *p*-Ns azide (entries 6–8).

Subsequently to this, we examined aziridination using SES azide with expectation that the reaction with this azide would show different stereochemistry from that with *o*- or *p*-Ns azide, because alkyl- and aryl-sulfonyl groups were considered to interact with the salen ligand differently from each other.[11] Fortunately, complex **3** was found to catalyze aziridination using SES azide as efficiently as the reaction with *o*- or *p*-Ns azide. Furthermore, enantioselectivity was improved to some extent, as compared with the reaction with *o*- or *p*-Ns azide (entries 9–11).[12] It should be noted that complexes **1** and **2** were less efficient also for the aziridination with SES azide: reactions of styrene in the presence of 1 mol % of complex **1** or **2** at room temperature for 12 h afforded the corresponding SES-protected aziridine in 10% yield (TON = 10) with 89% ee or in 67% yield (TON = 67) with 88% ee, respectively. The reactions of other terminal conjugated olefins with SES azide also proceeded with high enantioselectivity (entries 12 and 13). The aziridination of 1-octene was slow even at elevated temperature, but it showed good enantioselectivity of 77% ee (entry 14). The reaction of indene proceeded with excellent selectivity, albeit with moderate TON (entry 15). The *N*-SES group can be deprotected under mild conditions and it has been reported that chiral *N*-SES-protecting aziridines can be converted to the corresponding aziridines without diminishing their enantiomeric purity.[3g]

In conclusion, we were able to achieve highly enantioselective aziridination using 2-(trimethylsilyl)ethanesulfonyl azide as the nitrene precursor with reasonably designed Ru(salen)(CO) complex **3** as catalyst. Since the *N*-SES group can be readily removed, the present reaction provides a useful method not only for synthesizing *N*-sulfonylated aziridines but also for preparing non-*N*-protected ones under mild conditions.

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12. Typical procedure for enantioselective aziridination of styrene with SES azide: Ru(salen)(CO) complex **3** (0.6 mg, 0.5 μmol) was dried twice by azeotropical concentration of its toluene solution (0.25 mL) in vacuo under nitrogen atmosphere. Then, MS 4 Å (10 mg), styrene (5.7 μL, 0.05 mmol), 2-bromonaphthalene (2.0 mg, as the internal standard), and dichloromethane (0.25 mL) were added to the dried complex **3**. After stirring for 0.5 h at room temperature, SES azide (9.6 μL, 0.05 mmol) was added to the suspension at 0 °C and stirred for another 12 h at the temperature. The reaction mixture was filtrated through a Celite pad and evaporated. TON of Ru(salen) complex **3** was determined by ^{1}H NMR (400 MHz) analysis of the filtrate. Then, the filtrate was chromatographed on silica gel (hexane–ethyl acetate = 10/1–5/1) to give *N*-[2-(trimethylsilyl)ethanesulfonyl]-2-phenylaziridine in 99% yield (92% ee). The enantiomeric excess was determined by HPLC analysis using DAICEL CHIRALCEL OJ-H (hexane–*i*-PrOH = 97/3, 1.0 mL/min, $t_{major} = 17.8$ min and $t_{minor} = 28.0$ min).
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