Direct N-H/N-Me Aziridination of Unactivated Olefins Using O-(Sulfonyl)hydroxylamines as Aminating Agents

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Supporting Information

ABSTRACT: Unactivated aziridines are the core substructures in a plethora of bioactive natural products and serve as building blocks in organic synthesis. Despite this, very limited methods are available to access them directly from olefins, as most of the known methods are devoted to their activated counterparts. Herein, we have developed a highly efficient Rh(II)-catalyzed method for the direct preparation of unactivated aziridines from olefins using O-(sulfonyl)hydroxylamines as the aminating agent. The reactions proceed with a high stereospecificity.

Unactivated aziridines (N-H/N-Me) are in high demand because of their presence in many natural, semisynthetic, and synthetic bioactive molecules.1 They also serve as important building blocks in organic synthesis because of their remarkable reactivity via ring opening, ring expansion, and rearrangements.2 The regio- and stereospecific ring opening of unprotected (unactivated) aziridines with different nucleophiles (N, O, S, C) offers various functionalized unprotected scaffolds such as amino alcohols, diamines, thioamines, haloamines, etc.3 Whereas the methods for activated aziridine (e.g., N-Ts, N-Ns, N-acyl) preparation from alkenes are well-established, the direct method for accessing nonactivated aziridines is less explored, and most of these methods are multistep (Scheme 1).4,5 In 2014, Falck, Kürti, Ess, and co-workers (including the corresponding author of this paper) reported the first direct method for the preparation of N-H and N-Me aziridines from alkenes using 2,4-dinitrophenyl hydroxylamine (DPH) as the aminating agent in the presence of a rhodium catalyst (Du Bois catalyst) (A, Figure 1).6 This elegant method requires DPH in a stoichiometric amount that has several intrinsic drawbacks. For instance, the byproduct, 2,4-dinitrophenol (DNP), interferes via an undesired ring opening reaction. Both DPH and DNP are relatively unstable/explosive in nature due to a high NO2/C ratio, and DNP occasionally coelutes along with the product during column chromatography. Improving their previous method, Kürti et al. demonstrated another protocol using hydroxylamine-O-sulfonic acid (HOSA), instead of DPH, as the aminating reagent in the presence of 1.2 equiv of pyridine and the same rhodium catalyst (B, Figure 1).7 This modification could overcome the drawbacks of their previous method to a great extent; however, (i) it necessitated the use of 1.2 equiv of pyridine; (ii) column chromatography was still necessary, and (iii) it required the use of a relatively costly hexafluoroisopropanol (HFIP) as the solvent.

We were interested to develop an atom-economical, additive/base-free and possibly a column-chromatography-free method, as the strained aziridine rings frequently open during silica gel purification. To achieve these objectives, the aminating reagent desirably should (i) exist in a...
Cu(acac)₂ could catalyze the reaction to produce 3a in excellent yields (93%, entry 10). The screening of various other solvents under a condition similar to that of entry 10 had a detrimental effect. Both NhMe and Nh aziridines from alkenes using N-methyl-O-tosylhydroxylamine (3a) and 2,4,6-Me₃C₆H₃S-(O)₂ONH₂ (3b) as the aminating reagents, respectively.

Our study for Nh-Me aziridination began using methyl oleate 1a as the model substrate in the presence of 3a as the aminating agent in 2,2,2-trifluoroethanol (TFE) (Table 1).

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<th>yield (%)</th>
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<td>Cu(OAc)₂ (5 mol %)</td>
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<td>35</td>
</tr>
<tr>
<td>5</td>
<td>Cu(acac)₂ (5 mol %)</td>
<td>TFE</td>
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</tr>
<tr>
<td>6</td>
<td>FeSO₄·7H₂O (5 mol %)</td>
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"Reactions conditions unless otherwise mentioned: 1a (0.25 mmol), 3a (1.2 equiv), catalyst (1.0 mol %), solvent, rt. Yields are the isolated yield after an aqueous workup using saturated NaHCO₃ aqueous solution. Column purification was required. A mixture of TFE/CHCl₃ (1:1) was used as the solvent.

Table 1. Reaction Condition Optimization

Under this condition, both Fe(II)- and Fe(III)-based catalysts did not produce the desired product (entries 1 and 2). Whereas CuBr was found to be ineffective, Cu(OAc)₂ and Cu(acac)₂ could catalyze the reaction to produce 2a in 20–35% yield (entries 3–5). The yield improved significantly to 52% with FeSO₄·7H₂O (entry 6). Switching to various Rh-based catalysts further improved the yield of the reaction, eventually giving the desired product in excellent yield (96%) with Rh₂(esp)₂ in 30 min (entry 9). Decreasing the catalyst loading from 5 to 1 mol % did not affect the yield significantly (93%, entry 10). The screening of various other solvents under a condition similar to that of entry 10 had a detrimental effect on the reaction outcome (entries 11–15). To our delight, a simple workup using saturated NaHCO₃ aqueous solution completely removed the byproduct (TsOH), giving the desired product with good purity (by NMR).

To explore the scope of this method, a variety of alkenes were evaluated under the standard condition (as in entry 10, Table 1). Both cis- and trans-alkenes reacted well within an hour to give the corresponding aziridines in excellent yields (2a and 2b, Scheme 2). Olefins bearing even unprotected hydroxy group smoothly aziridinated with 91% (2c) isolated yield, whereas its TBS-protected derivative produced 2d in 95% yield at a lower reaction temperature. This TBS-protected alkene/aziridine was partially deprotected by stirring the reaction at room temperature. Cyclic alkene also participated in the reaction, affording 2e with 96% yield. Switching to a terminal alkene required a minor variation in the reaction condition as it was sluggish under the above optimized condition, and a prolongation of the reaction time under this condition led to the decomposition of the product. This reaction proceeded well with a slightly higher Rh catalyst loading of 5 mol % and at a lower reaction temperature (−10 °C), giving 2f in 63% isolated yield.

We next investigated the regioselectivity of the reaction using geraniol, which exclusively aziridinated at C₆−Δ₂,3) by an acetoxy or a benzoyloxy group toward aziridination. This observation was further supported by a much slower reactivity of the electron-deficient chalcone requiring 16 h for completion of the reaction (2k). A mixture of TFE and CHCl₃ (1:1) was used as the solvent for conjugated diene...
ester also, the aziridination occurred at the distal (Δ3,4) double bond selectively (2j, 58% yield). Both electron-rich as well as electron-deficient trisubstituted styrenes smoothly reacted to give the desired products (2l and 2m) in good yield, albeit the reaction was slower in the case of electron-deficient styrene. Tetra-substituted olefin, like β-ionone, failed to react under this optimized condition for N-Me (as well as for N-H) aziridination. It is worth noting that all the reactions proceeded with high stereospecificity and without formation of any allylic aminated side product.

After demonstrating the method for N-Me aziridination, we turned our attention to the direct N-H aziridination of alkenes. The literature survey and our own studies using the unprotected analogue of 3a (TsONH2) to achieve N-H aziridination was not successful as this reagent was unstable under this condition. A 2,4,6-trimethyl derivative of tosyl hydroxylamine (3b, Scheme 3) was found to be a good aminating agent under a condition similar to those in Scheme 2. Under this condition, different alkenes reacted well to give the desired products in good to excellent yield. For example, methyl oleate furnished the N-H aziridine 4a in 83% yield. Geranyl acetate and (2E,4Z)-ethyl dec-2,4-dienoate (a conjugated diene ester) afforded 4b (85% yield) and 4c (38% yield), respectively, as a single regioisomer. Simple as well as substituted styrenes were good substrates for this reaction at lower temperature to give the corresponding N-H aziridines in good yield (4d and 4f). β-Naphthylstyrene was also examined to obtain 4e in 64% yield. Chalcone reacted slowly to give the corresponding aziridine in 35% yield (4g). We also examined our reaction on a complex substrate like cholester. Under the optimized condition with TFE as the solvent, only a minor conversion was observed; the yield improved dramatically when a mixture of TFE/CHCl3 (1:1) was used as the solvent (4h, 70% yield), although the reaction took a longer time to complete (36 h). We expect these reactions to follow the same mechanistic pathway as previously proposed by Falck, Kürti, and Ess.

In conclusion, we have developed a direct, stereospecific Rh(II)-catalyzed N-H/N-Me aziridination method for alkenes using O-(sulfonyl)hydroxylamines as the aminating agents. These reagents do not generate explosive/interfering by-products and do not require base (pyridine) as an additive. This method provides various unactivated aziridines in good to excellent yield, and N-Me aziridines, in many cases, could be isolated with high purity just after an aqueous workup. Even highly reactive and labile functional groups like ketone, ester, alcohol, and silyl were well-tolerated. The reactions proceeded with a good chemoselectivity as neither the undesired amination nor the nitrene insertion on the aromatic ring was observed.

### EXPERIMENTAL SECTION

#### General Information

Unless otherwise specified, all reactions were carried out under an open atmosphere in a round-bottom flask. All aldehydes were of commercial quality and used without further purification. Olefins 1b, 1i, 1m, and β-naphthylstyrene were prepared following a known literature procedure.10 Solvents were dried and distilled following the standard procedures. TLC was carried out on precoated plates (Merck silica gel 60, 254), and the spots were visualized with UV light or by charring the plates dipped in PMA or KMNO4 solution. The compounds were purified by flash column chromatography using silica gel (230–400 mesh) with distilled solvents. 1H and 13C NMR spectra were recorded with 400 and 100 MHz instruments, respectively, in CDCl3 as the solvent. Chemical shifts (δ) are given in parts per million. The residual solvent signals were used as references (CDCl3: δ H = 7.26 ppm, δ C = 77.0 ppm). High-resolution mass spectrometry (HRMS) was performed on an agilent 6530 Q-TOF using electrospray ionization (ESI) and a time-of-flight (TOF) analyzer, in positive-ion or negative-ion detection mode.

#### General Procedure for N-H and N-Me Aziridination

To a round-bottom flask equipped with a magnetic stirring bar were added alkene 1 (0.5 mmol), aminating agent 3a or 3b (1.2 equiv), and TFE (2 mL) at room temperature. To this stirred solution was added Rh2(esp)(1 mol %), TFE (2.0 mL), rt. Yields are isolated after concentration of the organic layer in vacuo was purified by gel column chromatography to give the pure desired product.

#### Purification Method for Scheme 2

The organic layer was concentrated in vacuo to afford the pure desired product 2, unless reported otherwise.

#### Purification Method for Scheme 3

The crude product obtained after concentration of the organic layer in vacuo was purified by silica gel column chromatography to give the pure desired product 4 using 1% Bu3N in EtOAc/hexane or MeOH/CH2Cl2 as an eluent.

- **(E)-3,7-Dimethylocta-2,6-dienyl 4-Nitrobenzoate (1j).** To a solution of geraniol (200 mg, 1.29 mmol) and p-nitrobenzoyl chloride (289 mg, 1.54 mmol) in CH2Cl2 (15 mL) at 0 °C were added pyridine (136 µL, 1.54 mmol) and DMAP (18 mg, 0.15 mmol), and the reaction was stirred at room temperature for 18 h. After completion of the reaction, CH2Cl2 (10 mL) was added and the organic layer was washed with water (2 × 5 mL) and brine solution (5 mL). The organic layer was dried over anhydrous Na2SO4, concentrated in vacuo, and the crude product was purified by silica gel column chromatography (2% EtOAc in hexane) to give the title compound as a thick oil (325 mg, 83%). TLC Rf = 0.5 (3% EtOAc in hexane); 1H NMR (400 MHz, CDCl3) δ 8.28–8.23 (m, 2H), 8.22–8.17 (m, 2H), 7.59–7.52 (m, 1H), 5.10–5.04 (m, 1H), 4.87 (d, J = 7.1 Hz, 2H), 2.14–2.03 (m, 4H), 1.76 (s, 3H), 1.65 (s, 3H), 1.58 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 164.16, 150.4, 143.3, 135.8, 131.8, 130.6, 123.5, 123.4, 117.6, 62.7, 39.4, 26.2, 25.6, 17.6, 16.5;
Following the general aziridination procedure, the title aziridine was prepared following the general aziridination procedure, and the crude product was obtained as a colorless oil (89 mg, 85% yield), whose spectral data were in accord with the literature values.

7-Methyl-7-azabicyclo[4.1.0]heptanes (2e). Following the general aziridination procedure, the title aziridine was obtained as a light yellow oil (53 mg, 96% yield): TLC Rf = 0.4 (50% EtOAc in hexane), whose spectral data were in accord with the literature values.

1-(1-Methyl-1-aziridin-2-yl)nonan-1-ol (2f). The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu3N/EtOAc/hexane (1:5:94) as an eluent to give the title compound as an oil (129 mg, 83% yield), whose spectral data were in accord with the literature values.

1,2,2-Trimethyl-3-(4-nitrophenyl)aziridine (2m). The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu3N/EtOAc/hexane (1:5:94) as an eluent to give the title compound as a white solid (89 mg, 85% yield): TLC Rf = 0.5 (10% EtOAc in hexane); 1H NMR (400 MHz, CDCl3) δ 8.12 (m, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.49 (t, J = 7.7 Hz, 2H); 3.27–2.73 (m, 2H), 3.53 (d, J = 2.4 Hz, 1H), 1.90 (d, J = 2.2 Hz, 1H), 2.67 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 194.1, 137.9, 137.2, 133.5, 133.2, 128.7, 128.5, 128.4, 127.5, 48.7, 48.5, 38.6; HRMS (ESI) m/z [M + H]+ calc for C18H25N2O4 333.1815, found 332.1853.

2-Methyl-2-phenylaziridine (4d). The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu$_3$N/ EtOAc/hexane (1:19:80) as an eluent to give the title compound as a colorless oil (37 mg, 55% yield): TLC $R_f$ = 0.3 (50% EtOAc in hexane), whose spectral data were in accord with the literature values.

(E)-2-Methyl-3-(naphthalene-2-yl)aziridine (4e). The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu$_3$N/EtOAc/hexane (1:19:80) as an eluent to give the title compound as a colorless oil (59 mg, 64% yield): TLC $R_f$ = 0.19 (50% EtOAc in hexane), whose spectral data were in accord with the literature values.

(3-(4-Chlorophenyl)aziridin-2-yl)(phenyl)methanone (4g). The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using Bu$_3$N/EtOAc/hexane (1:19:80) as an eluent to give the title compound as a light yellow sticky solid (45 mg, 35% yield): TLC $R_f$ = 0.5 (30% EtOAc in hexane), whose spectral data were in accord with the literature values.

Aziridinylcholestan-3-β-diol (4h). The product was prepared following the general aziridination procedure, and the crude product was purified by silica gel column chromatography using EtOAc/ hexane (60:40) as an eluent to give the title compound as an off white solid (73 mg, 70% yield). $^1$H and $^{13}$C NMR data were in accord with the literature values.

**REFERENCES**


