[3+2] Cycloaddition of Aziridines and Alkenes Catalyzed by a Cationic Manganese Porphyrin

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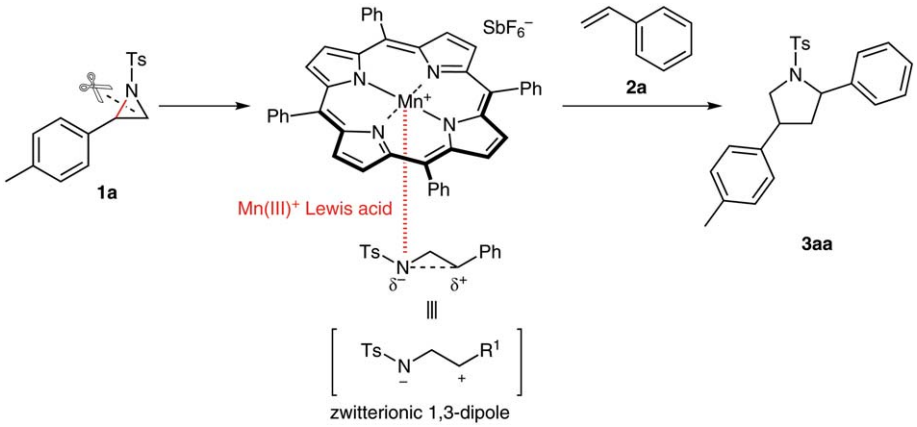
Abstract: A formal [3+2] cycloaddition between aziridines and alkenes to give the corresponding pyrrolidines was successfully carried out in the presence of a cationic manganese porphyrin catalyst. The use of the porphyrin catalyst allowed, for the first time, styrene derivatives to react with aziridines.

Key words: cycloadditions, manganese, porphyrins, heterocycles, catalysis, alkenes, ring expansion

Aziridines are three-membered nitrogen-containing heterocyclic compounds that are stable but inherently reactive, because of their ring-strain energy.[1] As a result, aziridines have attracted considerable attention as synthetic building blocks and, through ring opening, they have been used as 1,3-dipoles in formal [3+2] cycloaddition reactions with unsaturated compounds or carbonyl compounds to form five-membered heterocyclic scaffolds, such as pyrrolidines, imidazolines, and oxazolidines.[2–5] In this context, Lewis acids have been demonstrated to activate aziridines efficiently, generating 1,3-dipoles by ring opening, thereby effecting stereo- and regioselective [3+2] cycloadditions. The related Lewis acid catalyzed reaction in which aziridines are catalytically activated in situ to generate 1,3-dipoles for [3+2] cycloaddition is of great significance in heterocycle synthesis; however, such catalytic reactions have been successful only with a limited range of co-reactants, such as vinyl ethers and allylsilanes.[6] Here, we report a [3+2] cycloaddition of aziridines with alkenes in the presence of a cationic manganese porphyrin catalyst to afford pyrrolidines. The use of the cationic manganese porphyrin catalyst allows, for the first time, styrene derivatives to react with aziridines.

We initially surmised that *N*-sulfonylated aziridines might be activated by a cationic manganese porphyrin complex to generate a zwitterionic 1,3-dipole precursor that would undergo formal [3+2] cycloaddition with alkenes to give pyrrolidines (Scheme 1).[7–12] Indeed, the cycloaddition of 2-(4-tolyl)-1-tosylaziridine (**1a**) with styrene (**2a**) in the presence of cationic 5,10,15,20-tetraphenylporphyrin (TPP) manganese hexafluoroantimonate catalyst (5 mol%) in 1,2-dichloroethane at 100 °C for twelve hours gave the corresponding pyrrolidine **3aa** in 75% yield as a diastereomeric mixture (Table 1, entry 1).[13] In attempts to optimize the counteranion of the manganese porphyrin catalyst, pyrrolidine **3aa** was obtained in 65% and 54% yield when triflate and tetrafluoroborate ions, respectively, were introduced as counteranions (entries 2 and 3); however, the reaction was retarded when a chloride ligand was present in the manganese porphyrin catalyst (entry 4). Other solvents, such as toluene, 1,4-dioxane, or acetonitrile, gave reduced yields of **3aa** (entries 5–7), as did the use of silver hexafluoroantimonate instead of the cationic manganese porphyrin catalyst (entry 8). Note that the use



Scheme 1 Manganese porphyrin catalyzed [3+2] cycloaddition of aziridines and alkenes

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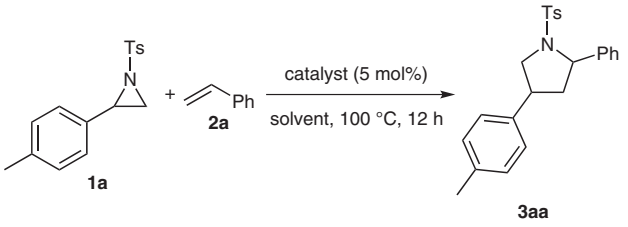
of a stoichiometric amount of boron trifluoride etherate instead of the manganese catalyst for the reaction of **1a** with **2a** at –78 °C resulted in the formation of **3aa** in 20% yield. In other words, the use of a conventional Lewis acid catalyst resulted in polymerization of **2a** in preference to [3+2] cycloaddition with **1a**, even at low temperatures.

Table 1 Manganese-Catalyzed Cycloaddition of **1a** and **2a**.



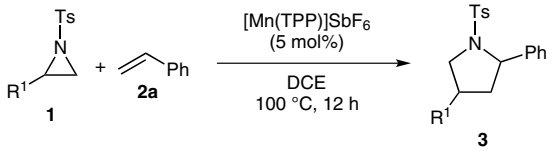
Entry	Catalyst	Solvent	Yield (%)[a]
1	[Mn(TPP)]SbF_6	DCE	75
2	[Mn(TPP)]OTf	DCE	60
3	[Mn(TPP)]BF_4	DCE	54
4	[Mn(TPP)]Cl	DCE	<1
5	[Mn(TPP)]SbF_6	toluene	45
6	[Mn(TPP)]SbF_6	1,4-dioxane	38
7	[Mn(TPP)]SbF_6	MeCN	<1
8	$AgSbF_6$	DCE	39

[a] Yield determined by NMR spectroscopy; mixture of two diastereomers.

Next, we examined the cycloaddition of various aziridines **1** with styrene (**2a**); the results are summarized in Table 2. The reactions of styrene with 2-arylaziridines containing electron-donating or electron-withdrawing substituents gave the corresponding pyrrolidines **3ba**–**fa** in good to moderate yields (entries 1–5). 2-(1-Naphthyl)-1-tosylaziridine (**1g**) similarly reacted with styrene (**2a**) to give pyrrolidine **3ga** (entry 6). However, 2-alkylaziridines such as 2-hexylaziridine or 2-cyclohexylaziridine did not undergo cycloaddition with styrene. Furthermore, neither *N*-alkylated aziridines nor *N*-*tert*-butoxycarbonyl aziridine reacted with styrene. These results suggest that the sulfonamide moiety is necessary to generate a zwitterionic intermediate, because of the greater stability of the nitrogen-centered anion.

Next, we examined the cationic manganese porphyrin-catalyzed formal [3+2] cycloaddition of aziridine **1a** with various alkenes **2** (Table 3). The reaction of aziridine **1a** with halostyrenes **2b** and **2c**, gave the corresponding substituted pyrrolidines **3ab** and **3ac** in 71% and 69% yield, respectively (entries 1 and 2). Likewise, the trimethylsilyl styrene derivative **2d** reacted with aziridine **1a** to give pyrrolidine **3ad** in 72% yield (entry 3). 1,1-Disubstituted styrene derivatives such as α-methylstyrenes **2e**–**g** reacted with aziridine **1a** to give the corresponding polysubstituted pyrrolidines **3** in good yields as diastereomeric mixtures (entries 4–6). Furthermore, the cycloaddition of aziridine **1a** with (1-cyclopropylvinyl)benzene (**2h**) gave pyrrolidine **3ah** in 70% yield (entry 7); no side-reaction involving cleavage of the cyclopropane ring was observed. Even exocyclic alkenes, such as 1-methylene-1,2,3,4-tetrahydronaphthalene (**2i**) or methylenecycloheptane (**2j**) reacted with aziridine **1a** to give the corresponding bicyclic pyrrolidines **3ai** and **3aj** (entries 8 and 9).

Table 2 Manganese-Catalyzed Cycloaddition of Aziridines **1b**–**g** with Styrene (**2a**)



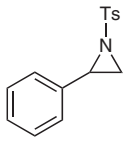
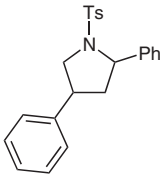
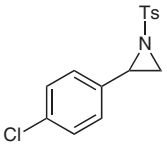
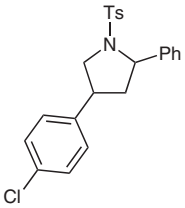
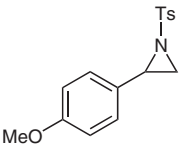
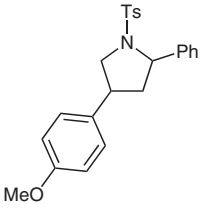
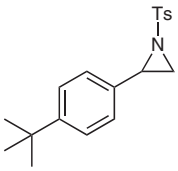
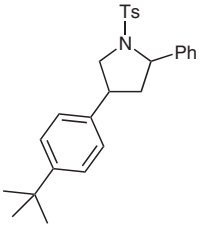
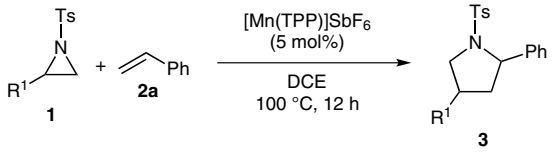
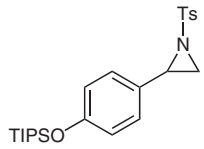
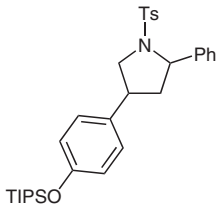
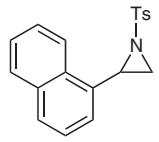
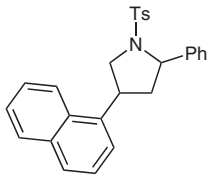
Entry	Aziridine	Product	Yield (%)[a]
1	 **1b**	 **3ba**	69
2	 **1c**	 **3ca**	63
3	 **1d**	 **3da**	65
4	 **1e**	 **3ea**	67

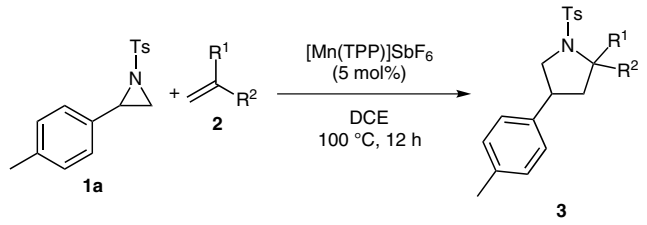
Table 2 Manganese-Catalyzed Cycloaddition of Aziridines **1b–g** with Styrene (**2a**) (continued)



Entry	Aziridine	Product	Yield (%)[a]
5	 **1f**	 **3fa**	72
6	 **1g**	 **3ga**	59

[a] Isolated yield of mixture of two diastereomers.

Table 3 Manganese-Catalyzed Cycloaddition of Aziridine **1a** and Alkenes **2b–j**



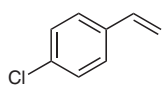
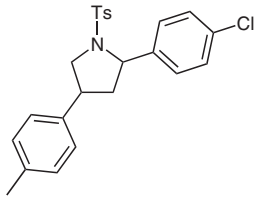
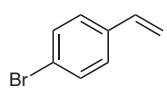
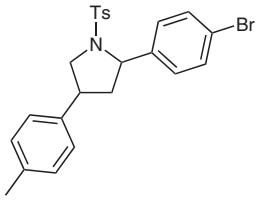
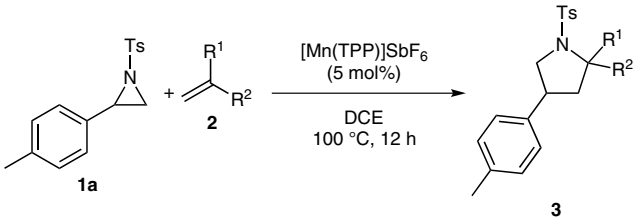
Entry	Alkene	Product	Yield (%)[a]
1	 **2b**	 **3ab**	71
2	 **2c**	 **3ac**	69

Table 3 Manganese-Catalyzed Cycloaddition of Aziridine **1a** and Alkenes **2b–j** (continued)



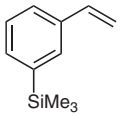
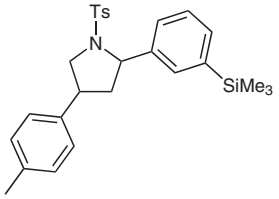
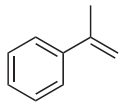
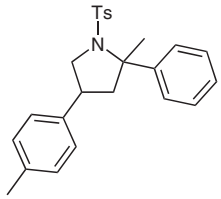
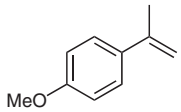
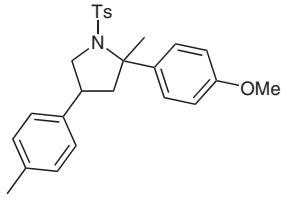
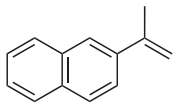
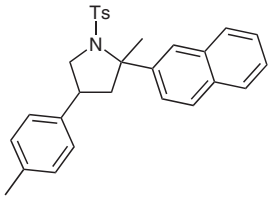
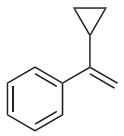
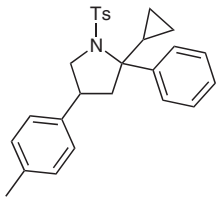
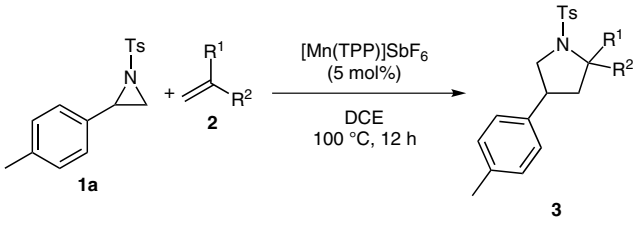
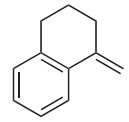
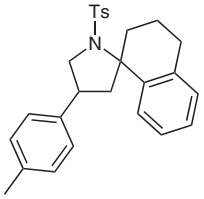
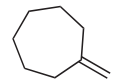
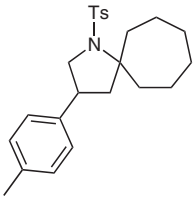
Entry	Alkene	Product	Yield (%)[a]
3	 **2d**	 **3ad**	72
4	 **2e**	 **3ae**	87
5	 **2f**	 **3af**	82
6	 **2g**	 **3ag**	79
7	 **2h**	 **3ah**	70

Table 3 Manganese-Catalyzed Cycloaddition of Aziridine **1a** and Alkenes **2b–j** (continued)

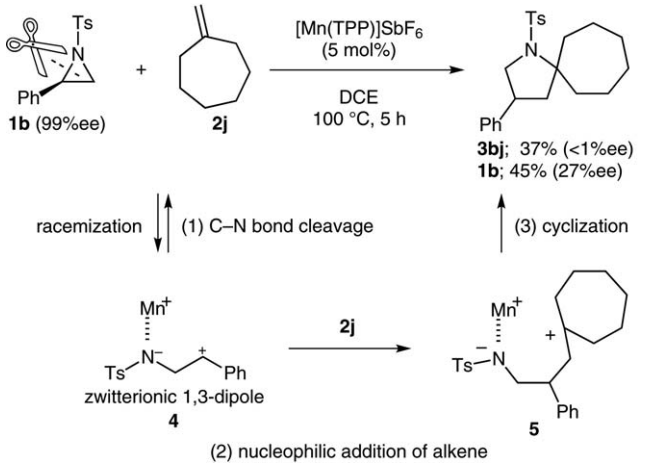


Entry	Alkene	Product	Yield (%)[a]
8	 **2i**	 **3ai**	86
9	 **2j**	 **3aj**	48[b]

[a] Isolated yields of mixture of two diastereomers.
[b] Single isomer.

To gain further insight into the manganese porphyrin-catalyzed cycloaddition, we examined the reaction of a chiral aziridine **1b** with an alkene (Scheme 2). The reaction of **1b** (99% ee) with methylenecycloheptane (**2j**) in the presence of the cationic manganese porphyrin gave cycloadduct **3bj** in 37% yield as a racemate; unreacted aziridine **1b** was recovered in 45% yield and 27% ee. The enantiomeric excess of the starting aziridine **1b** therefore decreased from 99% to 27% under the reaction conditions. These results suggest that the cycloaddition proceeds by a stepwise pathway that involves (1) the formation of the zwitterionic 1,3-dipole intermediate **4** through C–N bond cleavage of aziridine **1** by the cationic manganese porphyrin catalyst with loss of chirality, (2) nucleophilic addition of the π-bond of alkene **2j** to the positively charged benzylic position of intermediate **4** to give intermediate **5**, and (3) cyclization to afford cycloadduct **3bj** with regeneration of the active cationic manganese porphyrin catalyst.

In summary, we have demonstrated a cationic manganese porphyrin catalyzed [3+2] cycloaddition of aziridines with alkenes to afford pyrrolidines. The readily available metalloporphyrin complex, which contains a Lewis acidic cationic manganese center and a large π-conjugated planar aromatic structure, effectively catalyzed the reaction and promoted the generation of the zwitterionic 1,3-dipole precursor, thus realizing, for the first time, the cycloaddition of aziridines with styrene derivatives. Detailed studies to elucidate the mechanism underlying the unique reactivity of the cationic metalloporphyrin catalyst and efforts to improve the diastereoselectivity of the cycloaddition are underway.



Scheme 2 [3+2] Cycloaddition of chiral aziridine **1b** with methylenecycloheptane (**2j**)

Acknowledgment

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References and Notes

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(14) **Manganese Porphyrin Catalyzed [3+2] Cycloaddition of Aziridines and Alkenes; General Procedure**

A screw-cap vial was charged sequentially with [Mn(TPP)][SbF_6] (0.02 mmol, 19 mg), aziridine **1** (0.2 mmol), alkene **2** (0.6 mmol), and anhyd DCE (0.8 mL) in a dry box. The vial was sealed and the mixture was stirred at 100 °C for 12 h. The mixture was then diluted with 10:1 hexane–EtOAc (3 mL) and passed through a short pad of silica gel, which was washed with 1:1 hexane–EtOAc (2 × 10 mL). The mixture was then concentrated in vacuo to give a crude product that was purified by flash column chromatography [silica gel, (20 g, 2 × 15 cm), hexane–EtOAc (5:1)].

2-Phenyl-4-(4-tolyl)-1-tosylpyrrolidine (3aa)

Colorless oil; yield: 58 mg (75%); TLC: R_f = 0.40 (hexane–EtOAc, 5:1). IR (neat): 3028, 2954, 2923, 2870, 1599, 1494, 1348, 1338, 1182, 1027, 814, 662 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.74–7.73 (m, 1.8 H) 7.65–7.64 (m, 2 H), 7.42–7.24 (m, 13.3 H), 7.11–7.02 (m, 5.8 H), 6.93–6.92 (m, 1.8 H), 5.06 (d, *J* = 8.0 Hz, 0.9 H), 4.81 (dd, *J* = 6.5, 10 Hz, 1 H), 4.17–4.14 (m, 1 H), 4.02 (dd, *J* = 7.5, 9.0 Hz, 0.9 Hz), 3.52–3.41 (m, 1.9 H), 3.28 (dd, *J* = 9.5, 10.5 Hz, 0.9 H), 2.97–2.89 (m, 1 H), 2.69–2.65 (m, 1 H), 2.46 (s, 2.7 H), 2.44 (s, 3 H), 2.32 (s, 3 H), 2.30 (s, 2.7 H), 2.18–2.14 (m, 0.9 H), 2.11–2.00 (m, 1.9 H). ^{13}C NMR (125.7 MHz, $CDCl_3$): δ = 143.4, 143.2, 142.9, 142.6, 136.7, 136.6, 136.5, 135.9, 135.8, 134.8, 129.6, 129.5, 129.3, 129.2, 128.4, 128.3, 127.6, 127.4, 127.2, 127.1, 126.8, 126.8, 126.4, 126.1, 64.5, 63.0, 55.9, 55.1, 44.4, 43.3, 42.1, 41.0, 21.5, 21.4, 20.9, 20.9. HRMS (ESI^+): *m/z* $[M + H]^+$ calcd for $C_{24}H_{26}NO_2S$: 392.1679; found: 392.1663.