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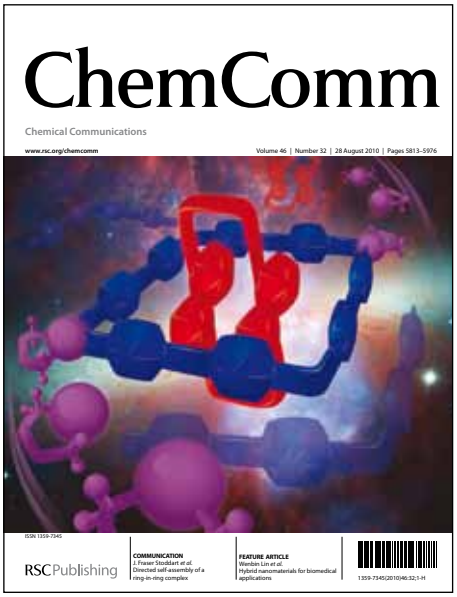

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Intermolecular (4+3) Cycloadditions of Aziridinyl Enolsilanes

Sze Kui Lam, Sarah Lam, Wing-Tak Wong, and Pauline Chiu*

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Under activation by strong Brønsted acids, aziridinyl enolsilanes undergo (4+3) cycloadditions with dienes to afford aminoalkylated cycloheptenones as products. The use of a highly polar medium such as nitroalkane facilitates high cycloaddition yields of up to 99%. Optically pure aziridinyl enolsilanes react to yield (4+3) cycloadducts with up to 99% ee.

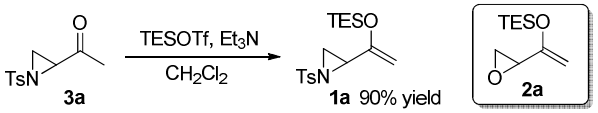
Functionalized cycloheptanoids are common subunits in natural products. There is a need for methods to construct these motifs under mild reaction conditions, and to produce them in a richly functionalized form with potential for further elaborations, to address the syntheses of many natural product targets, including alkaloids.[1]

The (4+3) cycloaddition is an efficient method to prepare functionalized cycloheptanes, where the classical reaction generated and employed 2-oxyallyl cations as dienophiles to undergo [$_\pi$4+$_\pi$2] cycloaddition with dienes.[2] Strategies to afford optically pure (4+3) cycloadducts[3] and novel methods to generate allyl cations as the three-carbon dienophile[4] are topics of ongoing research in this area.

We have reported on the silyl triflate-catalyzed (4+3) cycloaddition of epoxy enolsilanes reacting as dienophiles.[5,6] Both inter- and intramolecular (4+3) cycloadditions with cyclic dienes proceeded with facial and diastereoselectivity with respect to the epoxide stereochemistry to yield hydroxylated polycyclic ketones as products.

As an extension of this concept, we reasoned that strained rings other than epoxides could display a similar reactivity, and engender cycloaddition to afford alternatively functionalized cycloadducts. The importance of alkaloids in natural product chemistry led us to consider whether aziridinyl enolsilanes such as **1a** could also be similarly activated to yield dienophiles for (4+3) cycloadditions to afford amine-substituted cycloheptanones directly.[7]

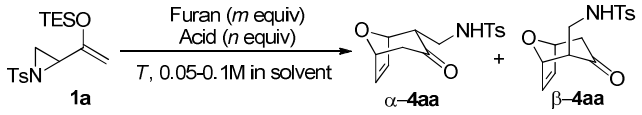
However, while epoxy enolsilanes **2a** yielded readily to ring cleavage under activation by silyl triflates, aziridinyl enolsilane **1a** was unreactive. This was not surprising, as the Si-O bond is much stronger than the Si-N bond, and silylation would be more effective for activation of epoxides than for aziridines. In fact, we could synthesize **1a** from ketone **3a** using TESOTf/Et_3N without concomitant decomposition of the aziridine (Scheme 1).



Scheme 1. Synthesis of aziridinyl enolsilanes.

Ultimately, we found that **1a** could be induced to undergo (4+3) cycloaddition by activation with a stoichiometric amount of TfOH, to afford a moderate yield of the endo and exo-cycloadducts α-**4aa** and β-**4aa** (Table 1, entry 1).[8] A sub-stoichiometric amount of acid resulted in incomplete reaction. We further reasoned that the formation of the protonated electrophilic intermediate would be promoted by the use of a polar medium. The use of propionitrile instead of dichloromethane as solvent indeed resulted in an improved yield (Table 1, entry 2). Nitroethane promoted a significant enhancement in yield to 86% when used as solvent (Table 1, entry 3). These results underscored that a polar, non-nucleophilic medium facilitates effective cycloadditions of aziridinyl enolsilanes **1**.

Table 1. Acid-mediated cycloaddition of **1a**



Entry	Solvent	*m*	Acid (*n* equiv)	*T* (°C)	Yield[a]	α-**4aa**:β-**4aa**
1	CH_2Cl_2	5	TfOH (1.1)	–90	56%	60:40
2	EtCN	5	TfOH (1.1)	–90	68%	38:62
3	$EtNO_2$	5	TfOH (1.1)	–90	86%	50:50
4	$EtNO_2$	5	TfOH (1.1)	–78	80%	52:48
5	$EtNO_2$	5	TfOH (1.1)	–45	68%	62:38
6	**$EtNO_2$**	**5**	**TFA (5.0)**	**–90**	**99%**	**55:45**
7	$EtNO_2$	3	TFA (5.0)	–90	92%	57:43
8	$EtNO_2$	1.5	TFA (5.0)	–90	84%	60:40
9	$EtNO_2$	5	TFA (5.0)	–78	95%	55:45
10	*i*-$PrNO_2$	5	TFA (5.0)	–90	99%	50:50
11	CF_3CH_2OH	5	TFA (5.0)	–44	--[b]	--
12	CH_2Cl_2	5	TFA (5.0)	–90	27%[c]	52:48

[a] Isolated yields; [b] 92% yield of **3a** isolated; [c] 72% yield of **3a** isolated.

It was also observed, however, that the strongly acidic reaction conditions induced polymerization that consumed the furan, and thus an excess of the diene was required for good cycloaddition yields. We then explored whether acids weaker than TfOH (pKa –14.9) could promote the same cycloaddition with less detrimental polymerization. After some investigations, we found that TFA (pKa +0.3) was a suitable acid. In the presence of 5 equivalents of TFA and using nitroethane as solvent, a near quantitative yield of **4aa** was obtained (Table 1, entry 6). The diene could be reduced from a 5.0 equivalent excess to 1.5 equivalents and still afford an 84% yield of cycloadducts, due to decreased polymerization and consumption of the diene under these conditions (Table 1, entries 7-8). Increasing the temperature to –78 °C resulted in a slightly diminished yield but further warming resulted in deleterious effects (Table 1, entries 3-5, 9). Nitroalkanes are

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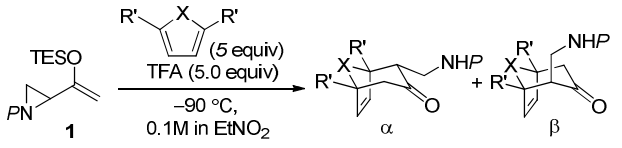
good solvents, but trifluoroethanol did not promote the desired reaction to any extent (Table 1, entries 10-11). Using TFA in dichloromethane resulted in mainly desilylation instead of cycloaddition (Table 1, entry 12).

With the optimized reaction conditions in hand, we explored the scope of aziridinyl enolsilanes **1** and dienes for the (4+3) cycloaddition. A range of sulfonylated aziridines **1a-d** were found to engage in cycloaddition, where increasing the steric bulkiness of sulfonyl group resulted in a slight decrease in the yield, but without any significant impact on the cycloadduct endo/exo ratios (Table 2, entries 1-6).

Table 2. Scope of the TFA-mediated (4+3) cycloaddition of **1a-g**



Entry	1	Diene R′	Diene X	Yield[a]	α:β
1	**1a**, P= Ts	H	CH_2	**4ab**, 93%	54:46
2	**1a**	Me	O	**4ac**, 25%[b]	79:21
3	**1a**	H	$(CH_2)_2$	**4ad**, 63%[c]	41:59
4	**1b**, P= Ms	H	O	**4ba**, 94%	52:48
5	**1c**, P= $MesSO_2$	H	O	**4ca**, 85%	57:43
6	**1d**, P= Trisyl	H	O	**4da**, 84%	57:43
7	**1e,** P= Boc	H	O	**4ea**, 53%[d]	53:47
8	**1e**	H	CH_2	**4eb**, 75%[d]	59:41
9	**1e**	H	$(CH_2)_2C$	**4ee**, 69%[d]	83:17
10	**1f,** P= CBz	H	O	**4fa**, 54%[d]	51:49
11	**1f**	H	CH_2	**4fb**, 79%[d]	58:42
12	**1g**, P= Piv	H	O	**4ga**, 39%[d]	49:51
13	**1g**	H	CH_2	**4gb**, 72%[d]	58:42

[a] Isolated yields; [b] 11% alkylated furan also obtained; [c] Isolated and methylated for separation, see SI; [d] Reaction promoted by 1.2 equiv. TFA.

Notably, we also found that aziridines protected by Boc (**1e**), CBz (**1f**) and Piv (**1g**) not only underwent reaction with acceptable yields and without concomitant deprotection, their cycloadditions were promoted without the need for a large excess of acid (Table 2, entries 7-13). For example, the treatment of **1e** with 1.2 equivalents of TFA and cyclopentadiene in nitroethane afforded a 75% yield of cycloadducts **4eb**, whereas the reaction of **1a** was largely incomplete under the same conditions. This can be attributed to the higher basicity of the aziridine protected as a carbamate or an amide, and hence are more effectively protonated and activated compared with a sulfonamide. However, **1** in which *P*= Bn did not yield to cycloaddition. The scope of the dienes that underwent cycloaddition included cyclopentadiene, spirocyclopentadiene, cyclohexadiene, as well as substituted furans.

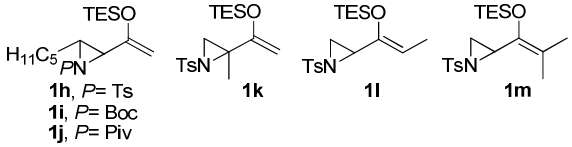


Figure 1. Substituted aziridinyl enolsilanes investigated

We also prepared and studied the cycloadditions of aziridinyl enolsilanes **1h-m** to examine the effects of substituents at C1, C2 and C4 of the enol ether (Figure 1).

Table 3. (4+3) Cycloadditions of **1h-m**

Entry	1	Diene	Cycloadducts		Yield[a] (dr)
1	**1h**	CpH	X=CH_2; α-**4hb**	X=CH_2; β-**4hb**	56% (60:40)[b]
2	**1i**	CpH	X=CH_2; α-**4ib**	X=CH_2; β-**4ib**	99% (60: 40)[c]
3	**1j**	CpH	X=CH_2; α-**4jb**	X=O; β-**4jb**	86% (65:35)[c]
4	**1k**	Furan	X=O; α-**4ka**	X=O; β-**4ka**	94% (87:13)
5	**1k**	CpH	X=CH_2; α-**4kb**	X=CH_2; β-**4kb**	68% (47:53)
6	**1k**	2-Me-furan	α-**4kf**	β-**5kf**	36% (87:13)
7	**1l**	CpH	α-**4lb**	β-**4lb**	74% (51:49)
8	**1m**	Furan	α-**4ma**	β-**4ma**	71% (93:7)
9	**1m**	CpH	α-**4mb**	β-**4mb**	72% (50:50)

[a]Isolated yields; [b]5% *epi*-**4hb** also obtained; [c]Reaction with1.2 equiv. TFA

All of aziridinyl enolsilanes yielded to cycloaddition under treatment with TFA, and most proceeded with good to excellent yields. Two diastereomeric cycloadducts from endo and exo modes of cycloaddition are generally obtained. Although many of the reactions showed no particular diastereoselectivity, a higher preference for endo product was observed in the cycloadditions of substituted enolsilanes **1k** and **1m**, where the dr was as high as 93:7 (Table 3, entries 4-6,8-9). This might be explained by steric preferences in the reactions of hindered substrates, as found previously for epoxides as well.[5] On the other hand, in analogy to the possible dienophiles in the corresponding reactions of the epoxy enolsilanes (Figure 2),[6] cycloaddition via the intermediacy of a softer, more oxyallyl cation-like intermediate C3 in the continuum, rather than through a hard, electrophilic intermediate such as C1, could also explain the higher endo selectivity. This would be consistent with the observation that significant endo selectivity was found only in the cycloadditions with furan, but not with cyclopentadiene (Table 3, entries 4 vs. 5, 8 vs 9), for which the minimization

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of the dipoles of the oxyallyl cation and furan in the transition state has been proposed as the rationale for endo selectivity.

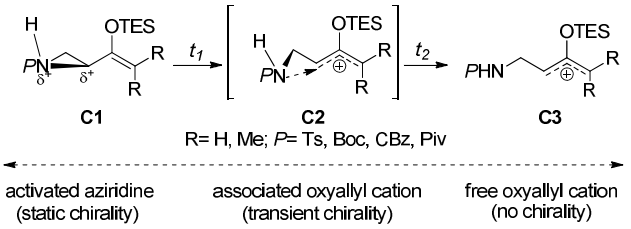
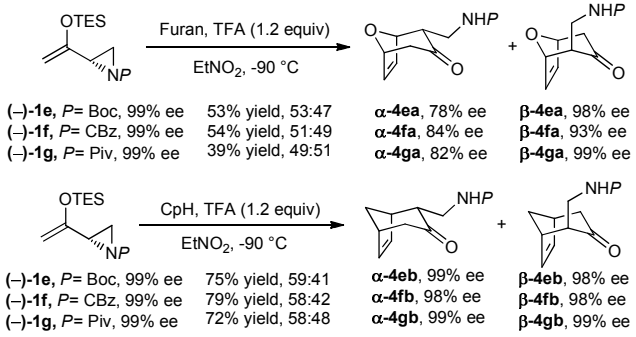


Figure 2. Possible dienophiles in the (4+3) cycloaddition

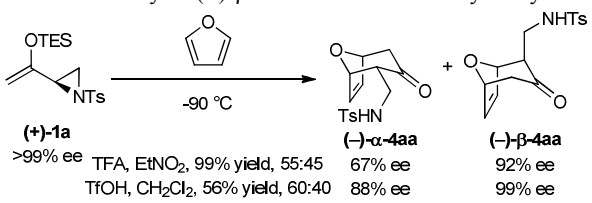
To differentiate between these explanations, and coinciding with the next stage of our program aimed at procuring optically enriched cycloadducts, we examined the cycloadditions of enantiomerically pure **1**. These enantiomerically enriched aziridines were synthesized from optically pure serine.†



Scheme 2. Cycloadditions of (-)-**1e-g**

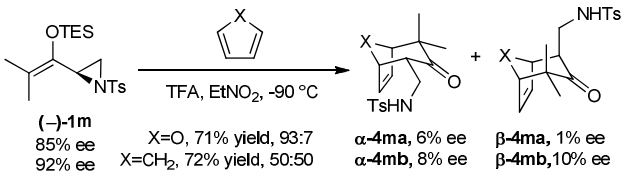
Indeed the cycloadditions of **1e-g** with either furan or cyclopentadiene generated optically enriched cycloadducts with up to 99% ee (Scheme 2), confirming the mechanism of this cycloaddition as proceeding through intermediates C1 or C2 with retention of stereochemical information, and not through the classical and necessarily achiral oxyallyl cations C3 (Figure 2, R= H). Therefore this aziridinyl enolsilane (4+3) cycloaddition constitutes a method to secure optically enriched, amine-substituted oxabicyclic and carbobicyclic ketones for asymmetric synthesis.

The (4+3) cycloadditions with furan were consistently lower in ee than with cyclopentadiene. This could be because furan is a less reactive diene and could not intercept C1 or C2 as effectively as cyclopentadiene. The enantiomeric excess can be partially recovered, however, by the use of a less polar medium than nitroethane (Scheme 3). The absolute stereochemistry of (–)-β-**4aa** was confirmed by x-ray.[9]



Scheme 3. Cycloadditions of (+)-**1a**

The cycloaddition of scalemic **1m**, however, produced cycloadducts **4ma** and **4mb** with almost no optical activity. Therefore the cycloadditions of **1m** probably proceeded through an intermediate with significant oxyallyl cation character, favoured due to additional substituents that stabilize C3 (Figure 2, R= Me). The endo selectivity was also a result of a more C3-like intermediate engaging in cycloaddition with furan.



Scheme 4. Cycloaddition of (-)-**1m**

We have shown for the first time that, promoted by Brønsted acid in nitroethane as solvent, aziridinyl enolsilanes react as dienophiles in the (4+3) cycloaddition with dienes, to directly afford amine-substituted cycloadducts with yields up to 99%. Enantiomerically-enriched cycloadducts of up to 99% ee could be obtained from optically enriched aziridinyl enolsilanes. Our efforts to understand the mechanism of the cycloaddition by experiment and computations, and to apply these cycloadditions to obtain chiral intermediates for the synthesis of bioactive alkaloids will be reported in due course.

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Notes and references

[a] *Department of Chemistry and State Key Laboratory of Synthetic Chemistry, The University of Hong Kong, Pokfulam Rd., Hong Kong, PR China. Fax: 852-28571586; Tel: 852-28598949; E-mail: pchiu@hku.hk*

† Electronic Supplementary Information (ESI) available: Experimental procedures and full characterization of all new compounds. See DOI: 10.1039/b000000x/

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9 Crystal data for (–)-β-**4aa**: $C_{15}H_{17}NO_4S$, Mw=307.36, Orthorhombic, space group $P\,2_12_12_1$ (#19), a = 5.0949 (2) Å, b = 12.0655 (4) Å, c =

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24.2090 (7) Å, β = 90.00°, V = 1488.19 (9) Å3, Z = 4, Dx = 1.372 Mg m-3, μ(Mo Kα)= 0.23 mm-1, F(000)= 648, T=296 K; crystal dimensions: 0.16 mm × 0.18 mm × 0.36 mm. Of the 11344 reflections that were collected, 2616 reflections were unique. (Rint = 0.0336); equivalent reflections were merged. All non-H atoms were refined anisotropically. R1 = 0.034, wR2 = 0.077. Crystallographic data for (–)-β-**4aa** have been deposited at the Cambridge Crystallographic Data Center, CCDC 976137.