Radical Intermediates

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Titanocene-Catalyzed Radical Opening of N-Acylated Aziridines

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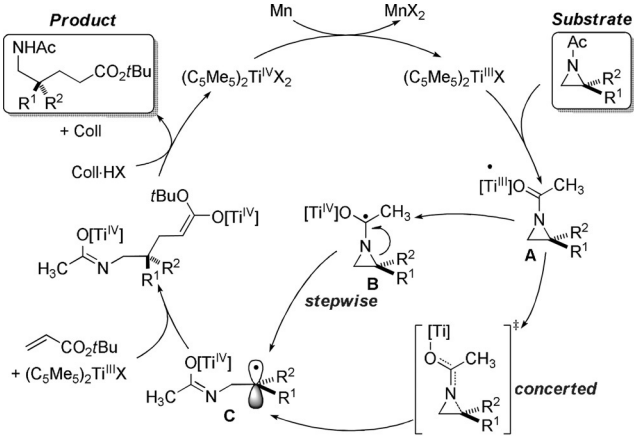
Abstract: *Aziridines activated by N-acylation are opened to the higher substituted radical through electron transfer from titanocene(III) complexes in a novel catalytic reaction. This reaction is applicable in conjugate additions, reductions, and cyclizations and suited for the construction of quaternary carbon centers. The concerted mechanism of the ring opening is indicated by DFT calculations.*

Aziridines are versatile building blocks for the preparation of functionalized amines. Ring opening of N-activated aziridines via S_N2 reactions is widely used and usually occurs at the less substituted carbon center.[1] Transition-metal-catalyzed cross couplings of N-sulfonylated aziridines with alkyl zinc reagents have emerged as a versatile C–C bond forming reaction[2] leading to the cleavage of either the benzylic C–N or the less substituted C–N bond. To the best of our knowledge, a general method for aziridine opening at the higher substituted carbon center does not exist.

Herein, we describe the first catalytic ring opening addressing this issue. It employs *N*-acyl aziridines as substrates for the generation of radicals **C** bearing β-amido substituents (Scheme 1). Electron transfer in the titanocene(III)–substrate complex **A**[3] is expected to result in the ring-opened carbon-centered radical **C**. This can occur either in a stepwise opening via aminoketyl radical **B** or in a concerted process. The potential of radicals **C** for the synthesis of functionalized amides is largely untapped. As yet, they have been generated from *N*-benzoylaziridines with stoichiometric amounts of Bu_3SnH or via electron transfer from arene radical anions.[4] They were reduced either in a radical-chain reaction or by a second electron transfer and protonation. In both cases, **B** was postulated as intermediate in the ring opening.

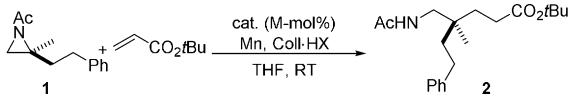
The key feature of *N*-acyl aziridines in our approach is their reduced amide resonance[5] that should render electron transfer in **A** more facile. Titanocene(III) complexes do not reduce typical amides.[6] The diminution of the amide resonance by the introduction of two electron-withdrawing groups on N has already been used for the generation of aminoketyl radicals derived from cyclic imides and related compounds.[7] This reaction uses stoichiometric amounts of SmI_2-containing water as an additive, a process likely proceeding through proton-coupled electron transfer given the energetics of a sequential process.[8]



Scheme 1. Proposed catalytic cycle for the trapping of radicals derived from *N*-acyl aziridines ([Ti^{IV}] = $(C_5Me_5)_2TiX$, X = Cl or Br).

We identified suitable conditions for the catalytic aziridine opening by trapping the putative radicals with *tert*-butyl acrylate (Scheme 1, Table 1).[9]

Table 1: Identification of suitable conditions for catalytic radical opening of *N*-acyl aziridines (Coll = 2,4,6-trimethylpyridine).[a]



Entry	Catalyst	mol%	Coll·HX	Yield [%]
1	$[Cp_2TiCl_2]$	10	Coll·HCl	22
2	$[(C_5H_4Me)_2TiCl_2]$	10	Coll·HCl	46
3	$[(C_5Me_5)_2TiCl_2]$	10	Coll·HCl	80
4	***[(C5Me5)2TiCl2]***	***10***	***Coll·HBr***	***82***
5	$[(C_5Me_5)_2TiCl_2]$	5	Coll·HBr	76

[a] Conditions: Catalyst (mol%), Mn (2.0 equiv.), Coll·HX (2.5 equiv.), *tert*-butyl acrylate (5.0 equiv.), **1** (0.125 M in THF), RT.

The standard conditions for titanocene-catalyzed epoxide opening (entry 1) failed to give a satisfactory yield of **2**.[10] Instead, the stronger reductant $[(C_5Me_5)_2TiCl]$ is required for efficient electron transfer to the carbonyl group (entries 2–4).[11] Catalyst loading can be reduced to 5 mol% without significant reduction in the yield of **2**. Coll·HCl and Coll·HBr are both suitable acids for mediating catalytic turnover.[12]

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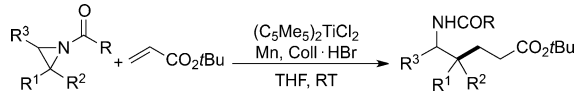
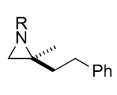
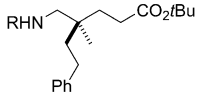
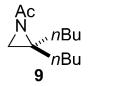
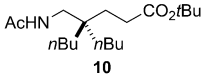
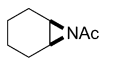
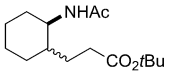
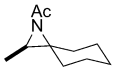
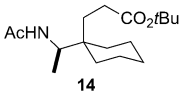
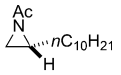
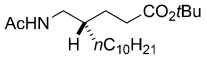
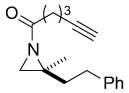
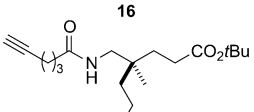
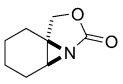
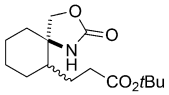
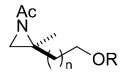
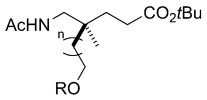
Table 2: Scope of the opening of *N*-acyl aziridines as function of their substitution pattern.[a]



entry	aziridine	product	yield [%]
			
1	R = Ac, **1**	R = Ac, **2**	82
2	R = CHO, **3**	R = CHO, **4**	65
3	R = CO_2Et, **5**	R = CO_2Et, **6**	77[b,c]
4	R = Boc, **7**	R = Boc, **8**	86[b,c]
5	 **9**	 **10**	86
6	 **11**	 **12**, *trans* : *cis* = 58:42	63[d,e]
7	 **13**	 **14**	51
8	 **15**	 **16**	48[e]
9	 **17**	 **18**	84
10	 **19**	 **20**, d.r. = 60:40	73[b,c]
			
11	n = 1, R = Bn, **21**	n = 1, R = Bn, **22**	83
12	n = 8, R = TBS, **23**	n = 8, R = TBS, **24**	77
13	n = 8, R = Piv, **25**	n = 8, R = Piv, **26**	68
14	n = 8, R = Bz, **27**	n = 8, R = Bz, **28**	66

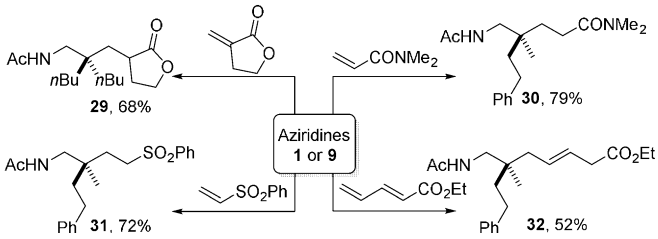
[a] Conditions unless otherwise noted: [(C_5Me_5)$_2$$TiCl_2$] (10 mol%), Mn (2.0 equiv.), Coll·HBr (2.5 equiv.), *tert*-butyl acrylate (5.0 equiv.), aziridine (0.125 M in THF), RT. [b] [(C_5Me_5)$_2$$TiCl_2$] (15 mol%). [c] 50°C. [d] [(C_5Me_5)$_2$$TiCl_2$] (20 mol%). [e] 70°C. Boc = *tert*-butyloxycarbonyl; Bz = benzoyl.

The generality of our reaction was investigated next (Table 2). First, we explored the influence of the carbonyl substituent. Due to a reduced stability of the substrate, the formyl group (entry 2) is inferior. Gratifyingly, aziridinyl carbamates (entries 3 and 4) were also efficient substrates at slightly higher temperature (50°C) through unprecedented electron transfer to a carbamate. The BOC-substituted substrate (entry 4) is of practical importance because it allows a straightforward amine synthesis after acidic removal of the protecting group.

The catalytic opening can be carried out with mono-, di-, and trisubstituted aziridines and results in the exclusive formation of the products derived from ring opening at the higher substituted carbon center. The functional-group tolerance of the reaction is high (entries 11–14). Thus, our method is broadly applicable and highly efficient for the synthesis of quaternary alkyl-substituted carbon centers. With **17** no cyclic product as a consequence of trapping by the alkyne unit was obtained.

With the strained tricyclic substrate **19**,[13] ring opening lead to the spirocyclic product **20** via a secondary radical. Consistent with the experiment, a similar mechanism was found by DFT calculations for the ring opening of tricyclic substrate **19**, but with a slightly lower barrier for the formation of the secondary radical due to ring-strain effects (see the Supporting Information for details).

The trapping of the aziridine-derived radicals is not confined to *tert*-butyl acrylate (Scheme 2). α-Methylenelactones, acrylamides, and vinylsulfones[14] can be employed to deliver the products in satisfactory yields. Interestingly, the use of ethyl (*E*)-penta-2,4-dienoate resulted in the formation of the (*E*)-β,γ-unsaturated ester **32** as single isomer.



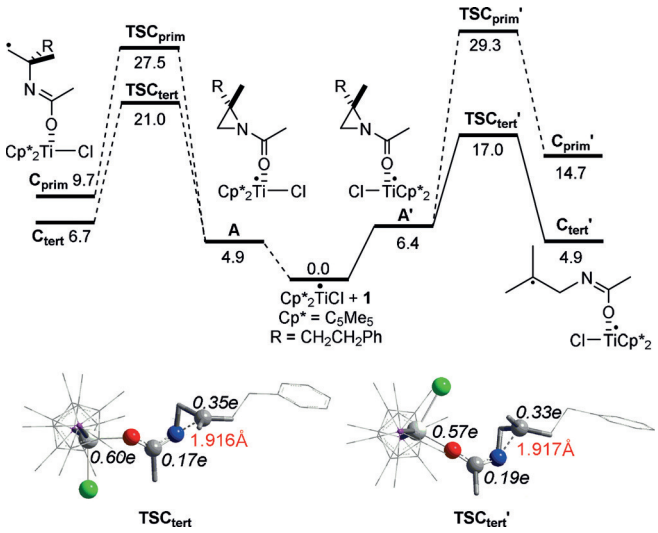
Scheme 2. Michael acceptors in the catalytic aziridine opening. Conditions: [(C_5Me_5)$_2$$TiCl_2$] (10 mol%), Mn (2.0 equiv.), Coll·HBr (2.5 equiv.), activated olefin (5.0 equiv.), THF, RT.

To understand the mechanism of the ring opening, we studied the reaction of **1** by DFT calculations (Scheme 3) at the TPSS-D3/def2-QZVP + COSMO-RS (THF)//TPSS-D3/def2-TZVP + COSMO (THF) level.[15]

The formation of the two complexes **A** and **A′**, which differ in structure by a rotation of the substrate by 180°, from [(C_5Me_5)$_2$TiCl] and **1** is exothermic but endergonic due to unfavorable entropy effects. Both complexes are similar in energy. The formation of the primary radicals $\mathbf{C_{prim}}$ and $\mathbf{C_{prim}'}$ is thermodynamically and kinetically disfavored. The transition states $\mathbf{TSC_{prim}}$ and $\mathbf{TSC_{prim}'}$ have a higher spin density (0.56 and 0.50 electrons, respectively) at the developing primary radical explaining the high free energy barrier $\Delta G^{\ddagger}$.

The formation of the tertiary radicals is thermodynamically unfavorable from **A** but slightly favored from **A′**. Moreover, $\mathbf{TSC_{tert}'}$ is noticeably lower in energy than $\mathbf{TSC_{tert}}$. This is due to reduced steric interactions, a lower spin density at the developing tertiary radical, and a higher spin density at Ti. For both $\mathbf{C_{tert}}$ and $\mathbf{C_{tert}'}$, trapping by *tert*-butyl acrylate has a lower $\Delta G^{\ddagger}$ than closure to **A** and **A′** (see the Supporting Information for details). This should result in an irreversible ring opening.

In none of the cases discussed above, we were able to locate an aminoketyl radical structure **B** (see Scheme 1). Therefore, our data are consistent with the titanocene-catalyzed ring opening of *N*-acyl aziridines occurring through

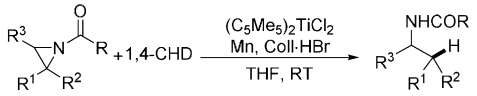


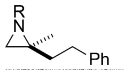
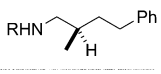
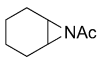
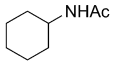
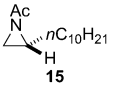
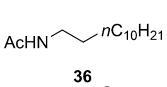
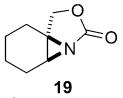
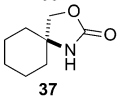
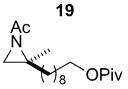
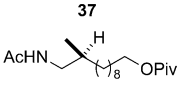
Scheme 3. At the TPSS-D3/def2-QZVP + COSMO-RS (THF) level computed free-energy paths (in kcal mol^{-1}) for the opening of **1**. Transition structures are shown with the respective crucial Ti (white), Cl (green), O (red), C (grey), and N (blue) atoms. TPSS-D3/def2-TZVP + COSMO (THF) computed Mulliken spin densities (> 0.1*e*, in italics) are indicated.

a concerted rather than a stepwise process as suggested for other cases.[4a–c]

1,4-cyclohexadiene (CHD) is an efficient H-atom donor for the reduction of radicals derived from *N*-acyl aziridines (Table 3). The regioselectivity of the ring opening to yield the less substituted amide or carbamate is complete except for **15** (entry 4), when a 90:10 mixture of regioisomers was obtained.

Table 3: Reduction of aziridines through hydrogen-atom transfer.[a]

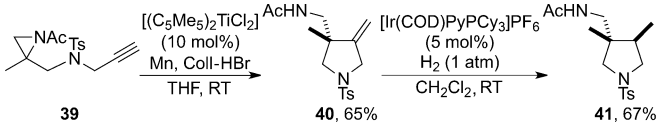


entry	substrate	product	yield [%]
			
1	R = Ac, **1**	R = Ac, **33**	76
2	R = Boc, **7**	R = Boc, **34**	84[b,c]
3	 **11**	 **35**	74[c,d]
4	 **15**	 **36**	55[b,c,e]
5	 **19**	 **37**	79[b,c]
6	 **25**	 **38**	78

[a] Conditions: [(C$_5$Me$_5$)$_2$TiCl$_2$] (10 mol%), Mn (1.5 equiv.), Coll·HBr (1.5 equiv.), 1,4-CHD (8.0 equiv.), aziridine (0.125 M in THF), RT. [b] [(C$_5$Me$_5$)$_2$TiCl$_2$] (15 mol%). [c] 50 °C. [d] [(C$_5$Me$_5$)$_2$TiCl$_2$] (20 mol%). [e] 90:10 mixture of primary and secondary acylamine.

The Bu$_3$SnH-mediated opening[4a] requires *N*-Benzoyl substitution and is less general.

N-Acyl aziridine derived radicals can also be used in a 5-*exo* cyclization with an alkyne (Scheme 4).[16] **40** was hydrogenated with Crabtree's catalyst[17] in high selectivity to furnish **41**, which may be of potential interest for the synthesis of biologically active substances.[18]



Scheme 4. Cyclization of aziridines with a pendant alkyne unit.

In summary, we have developed the first catalytic radical opening of N-acylated aziridines. The reaction is highly regioselective, has a broad substrate scope and functional-group tolerance, and can be used in cyclizations, reductions, and additions to activated olefins. Through DFT calculations we could show for the first time that the ring opening of *N*-acyl aziridines through electron transfer can proceed in a concerted manner.

Experimental Section

A heat-dried Schlenk tube was charged with Coll·HBr (2.5 equiv.) under Ar and the Schlenk tube was gently heated under vacuum. Mn (2.0 equiv.), [(C$_5$Me$_5$)$_2$TiCl$_2$] (0.1 equiv.), and THF were added. The mixture was stirred for 10 min. *tert*-Butyl acrylate (5.0 equiv.) followed by the aziridine (1.0 equiv, 0.125 M in THF) was added. After stirring at the indicated temperature for 16 h, the reaction mixture was filtrated through a plug of SiO$_2$ with EtOAc. The crude product was purified by flash chromatography on silica gel.

Acknowledgements

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Conflict of interest

The authors declare no conflict of interest.

Keywords: aziridines · conjugate addition · radical ring opening · reduction · titanocenes

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