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Iron(II)-catalyzed intramolecular aminochlorination of alkenes

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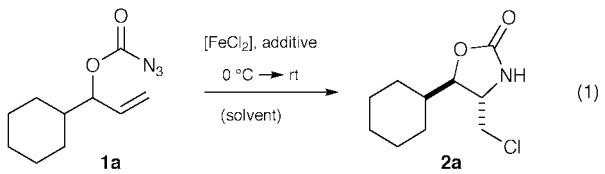
2-Alkenyloxycarbonyl azides undergo an efficient intramolecular Fe^{II}-catalyzed aminochlorination with TMSCl in EtOH and furnish the corresponding 4-(chloromethyl)-oxazolidinones (60–84% yield), presumably *via* a stepwise single electron transfer pathway.

The catalytic aziridination of alkenes is a topic of current scientific interest.[1,2] In particular, transition metal catalysts which allow a nitrene transfer to alkenes and which can be modified by chiral ligands have attracted considerable attention.[3] Research in our group has been directed towards the transfer of *N*-alkoxycarbonyl substituted nitrene fragments to nucleophiles. We have shown that the reaction of *tert*-butoxycarbonyl azide ($BocN_3$) with sulfides and sulfoxides is catalyzed by $FeCl_2$ (10–25 mol%) and yields the corresponding sulfimides and sulfoximides in moderate to good yields.[4] We have now studied the Fe^{II}-catalyzed intramolecular nitrogen transfer to alkenes using the corresponding 2-alkenyloxycarbonyl azides.

Substrates of this type are known to undergo an intramolecular aziridination under thermal conditions.[5] The strained aziridines primarily formed are ring-opened readily by nucleophiles. Metal-catalyzed versions of this aziridination reaction have not been reported. Initial experiments in our laboratories were carried out with the azide **1a**[6] [eqn. (1)].



In all cases we studied, the *trans*-4-(chloromethyl)-oxazolidinone **2a** was obtained as the major nitrogen transfer product. An aziridine intermediate was not observed. In CH_2Cl_2 and THF the reaction proceeded sluggishly. MeCN proved to be a superior solvent for the desired transformation (Table 1, entry 1). Since a source of chloride ions was essential to guarantee an effective catalytic cycle we screened several candidates. TMSCl finally turned out to be the additive of choice (entry 2). It was, however, not possible to obtain acceptable yields using 0.1 equiv. of the catalyst in MeCN (entry 3). In search of another solvent which would allow a decreased catalyst loading we found EtOH to be ideally suited (entry 6). With 10 mol% of the catalyst a product yield of 72% was achieved (entry 7). In some instances, variation of the additive or the solvent led to complete inhibition of the reactions (entries 4, 5 and 8).

Table 1 Fe^{II}-catalyzed intramolecular aminochlorination of substrate **1a**

Entry	Solvent	$FeCl_2$/ equiv.	Additive	Yield (%)[a]	*trans*:*cis*[b]
1	MeCN	0.5	—	59	95:5
2	MeCN	0.5	TMSCl[c]	63	95:5
3	MeCN	0.1	TMSCl[c]	24	96:4
4	MeCN	0.5	$FeCl_3$[c]	< 5	—
5	MeCN	0.5	H_2O[d]	< 5	—
6	EtOH	0.5	TMSCl[c]	70	90:10
7	EtOH	0.1	TMSCl[c]	72	91:9
8	MeOH	0.5	TMSCl[c]	< 5	—

[a] Yield of isolated product after chromatographic purification. [b] Ratio of the two oxazolidinone diastereoisomers as determined by ^1H NMR spectroscopy. [c] 1.5 equiv. of the additive were employed.. [d] A 9:1 (v/v) solvent mixture of MeCN–H_2O was used.

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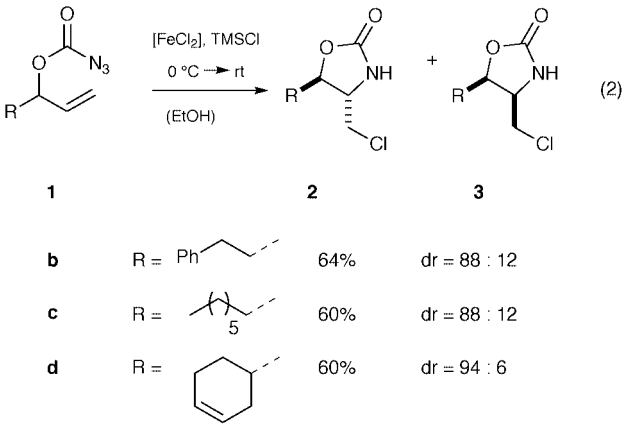
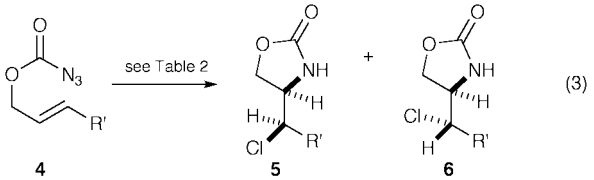
Under optimized conditions (0.1 equiv. $FeCl_2$, 1.5 equiv. TMSCl, EtOH)[7] other substrates **1** reacted equally well [eqn. (2)]. In the case of the azides **1b** and **1c**, which bear a smaller



primary alkyl group at the stereogenic center, the facial diastereoselectivity was slightly lower than with the secondary alkyl substituted substrates **1a** and **1d**. The product **2d** obtained from the diastereomeric mixure of the 3-cyclohexenyl-substituted substrate **1d** was as a mixture of two 4,5-*trans*-isomers due to the additional stereogenic center at the cyclohexene ring.

Mechanistically, we initially assumed an aziridination–ring opening sequence to be responsible for the formation of the 4-(chloromethyl)oxazolidinones **2** and **3**. We started to cast doubt on this idea when we studied the Fe^{II}-catalyzed reaction of the achiral (2*E*)-alkenyloxycarbonyl azides **4** [eqn. (3)]. One



would expect the aziridination to occur stereospecifically to yield a *trans*-aziridine, which would upon ring opening form the *erythro*-product **6**. Contrary to this expectation, the azide **4a** gave only a mixture of diastereoisomers (Table 2, entry 1). We conducted the same reaction in boiling 1,1,2,2-tetrachloroethane (TCE) in the absence of Fe^{II} and obtained exclusively a single product, albeit in much lower yield (entry 2). In this case an aziridine is known to be the intermediate[5b] and the ring opening occurs most likely by HCl, which is formed from TCE upon heating.[5a] Based on analogy with the reactions of azide **4b**

Table 2 Yields and diastereoselectivities determined in the intramolecular aminochlorination of 2-alkenyloxycarbonyl azides **4**

Entry	Substrate	R′	Meth1od	Yield (%)[a]	**5**:**6**
1	**4a**	Pr	$FeCl_2$ (EtOH)	84	49:51
2	**4a**	Pr	Δ*T* (TCE)	62	<1:99
3	**4b**	Ph	$FeCl_2$ (EtOH)	76	>99:1
4	**4b**	Ph	Δ*T* (TCE)	42	<1:99

[a] Yield of isolated product after chromatographic purification.

under the same two different conditions (*vide infra*), structure **6a** was assigned to this product. A thermodynamic equilibration was ruled out because the *erythro*-product **6a** did not interconvert to the *threo*-product **5a** upon treatment with $FeCl_2$.

The difference between the two reaction variants was even more dramatic when we used azide **4b** as the starting material. The Fe^{II}-catalyzed reaction delivered exclusively the *threo*-product **5b** (entry 3), whereas the thermal reaction furnished the *erythro*-product **6b** (entry 4). In this case the relative configuration of one diastereoisomer (**5b**) could be unambiguously proven by single X-ray crystallography[8] (Fig. 1).

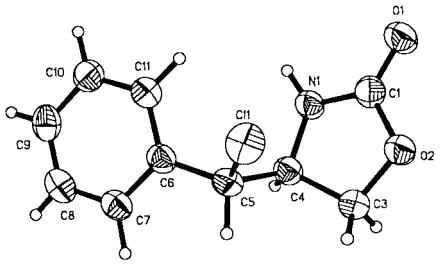
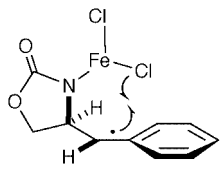


Fig. 1 A molecule of compound **5b** in the crystal.

These observations are in line with an Fe^{II}-catalyzed nitrogen transfer *via* radicals as intermediates. Apparently, the intermediate formed from $FeCl_2$ and the azide does not transfer the fragment to the alkene in a concerted fashion, but in a stepwise fashion. The reaction of **4a** is not stereospecific, as a free rotation can occur after N–C bond formation. A possible explanation for the high preference in favor of *threo*-product **5b** in the aminochlorination of substrate **4b** is shown below. The intermediate **7** formed from **4b** adopts the preferred conformation shown owing to 1,3-allylic strain; within this conformation intramolecular chloride transfer can occur diastereoselectively.



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If this picture is correct there is an obvious analogy between the reaction we study and intermolecular radical-type aminochlorination reactions of *N*-chloro-*N*-alkenyl amines and *N*-chloroalkenamides.[9] Mechanistic evidence might consequently be deduced from comparing the stereochemical outcome of these reactions with the results obtained by the Fe^{II}-catalyzed reaction of similar substrates. A direct comparison is not yet possible as reactions of *N*-chloro-*O*-alkenyl carbamates related to **1** have to the best of our knowledge not been reported.

In further work which is currently underway we plan to undermine our mechanistic hypothesis based on the above-mentioned analogy and based on suitable radical clocks.

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Notes and references

1 Review on the asymmetric synthesis of aziridines: H. M. I. Osborn and J. Sweeney, *Tetrahedron: Asymmetry*, 1997, **8**, 1693.

2 Some selected examples: D. A. Evans, M. M. Faul and M. T. Bilodeau, *J. Org. Chem.*, 1991, **56**, 6744; K. J. O'Connor, S.-J. Wey and C. J. Burrows, *Tetrahedron Lett.*, 1992, **33**, 1001; K. Noda, N. Hosoya, R. Irie, Y. Ito and T. Katsuki, *Synlett*, 1993, 469; D. A. Evans, M. M. Faul and M. T. Bilodeau, *J. Am. Chem. Soc.*, 1994, **116**, 2742; Z. Li, R. W. Quan and E. N. Jacobsen, *J. Am. Chem. Soc.*, 1995, **117**, 5889; P. Müller, C. Baud and Y. Jacquier, *Tetrahedron*, 1996, **52**, 1543; J. U. Jeong, B. Tao, I. Sagasser, H. Henniges and K. B. Sharpless, *J. Am. Chem. Soc.*, 1998, **120**, 6844.

3 Review: P. Müller, in *Advances in Catalytic Processes Vol. 2, Asymmetric Catalysis*, ed. M. P Doyle, JAI, , Greenwich, 1997, pp. 131–151.

4 T. Bach and C. Körber, *Tetrahedron Lett.*, 1998, **39**, 5015; T. Bach and C. Körber, *Eur. J. Org. Chem.*, 1999, 1033.

5 (*a*) S. C. Bergmeier and D. M. Stanchina, *Tetrahedron Lett.*, 1995, **36**, 4533; (*b*) S. C. Bergmeier and D. M. Stanchina, *J. Org. Chem.*, 1997, **62**, 4449.

6 The azides were prepared by successive treatment of the corresponding allylic alcohols with 1,1′-carbonyldiimidazole and NaN_3: P. Yuan, P. Plourde, M. R. Shoemaker, C. L. Moore and D. E. Hansen, *J. Org. Chem.*, 1995, **60**, 5360. **CAUTION**! Alkoxycarbonyl azides are potential explosives. Appropriate safety protection and utmost care are required while handling these compounds.

7 Representative procedure: A solution of **1a** (209 mg, 1.00 mmol) and TMSCl (163mg, 1.50 mmol) in dry ethanol (5 ml) was degassed with a stream of argon at 0 °C for 15 min. $FeCl_2$ (13 mg, 0.10 mmol) was added in one portion to the stirred solution. The formerly colorless reaction mixture turned yellow and nitrogen started to evolve. The solution was allowed to warm to room temperature and was stirred for another 20 h. It was then dissolved in EtOAc (20 ml) and washed with water (2 × 20 ml) and brine (20 ml). The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The brown residue was purified by chromatography on silica using pentane–*tert*-butyl methyl ether (2:8) as the eluent. A mixture of **2a** and **3a** was obtained as colorless crystals (156 mg, 72%, dr = 91:9). The analytical data were in agreement with the literature values (ref. 5).

8 *Crystal data* for **5b**: $C_{10}H_{10}ClNO_2$, *M* 211.64 g mol^{-1}, monoclinic, *a* = 789.0 (1), *b* = 583.8 (1), *c* = 2055.2 (1) pm, β = 94.175 (4)°; V = 944.1 (1) × 10^{-30} m^3, space group $P2_1/c$, *Z* = 4, λ = 3.358 mm^{-1}, reflections collected = 3750, independent reflections = 1922 [R_{int} = 0.0766], wR_2 = 0.1310, *R* = 0.0459 [$I > 2\sigma(I)$]. CCDC 182/1523.

9 Reviews: A. G. Fallis and I. M. Brinza, *Tetrahedron*, 1997, **53**, 17543; D. Savoia, in *Houben-Weyl Methoden der Organischen Chemie*, 4th edn., ed. G. Helmchen, R. W. Hoffmann, J. Mulzer and E. Schaumann, Thieme, Stuttgart, 1996, vol. E21, pp. 5265–5273.

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