Asymmetric Catalysis

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Catalytic, Enantioselective Ring Opening of Aziridines

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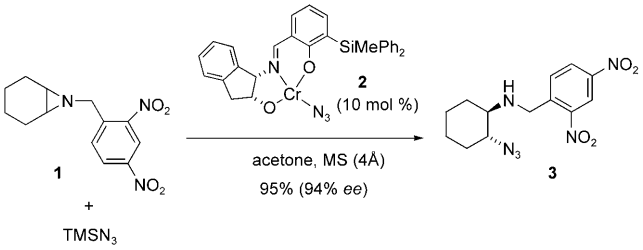
cooperative effects · homogeneous catalysis · nitrogen heterocycles · ring opening · small ring systems

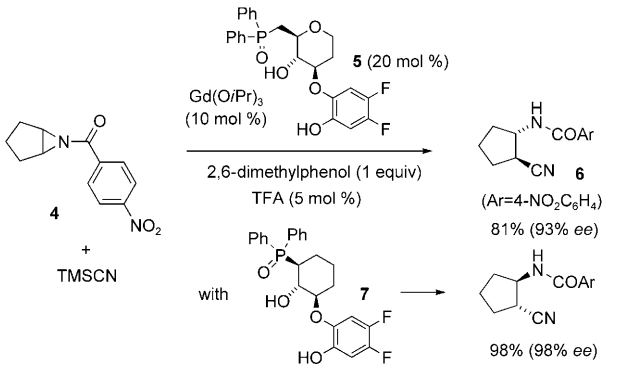
The asymmetric ring opening of *meso* epoxides is being used increasingly in the enantioselective synthesis of 1,2-difunctionalized fine chemicals.[1] However, until recently there was no efficient method for the related aziridines, which is surprising in view of the potential of this reaction, for example, in the direct synthesis of valuable, optically pure 1,2-diamines. In principle, owing to the similarly large ring strain, the ring opening of aziridines should be about as facile as that of epoxides, especially when the aziridine nitrogen atom is activated electronically by electron-withdrawing substituents, such as acyl or tosyl groups. However, the substituent on the N atom can be aligned either *cis* or *trans* to other ring substituents through pyrimidal inversion at this position, which leads to competitive transition states in the case of Lewis acid catalyzed reactions and can thus complicate a subsequent selective reaction.

Following isolated reports in the 1990s,[2] Jacobsen and co-workers described the first highly enantioselective ring opening of *meso* aziridines in 1999. Under the catalysis of the chiral chromium(III)–salicylimine complex **2**, *meso* *N*-benzylaziridines such as **1** reacted with trimethylsilyl azide to give 1,2-azidoamines such as **3** in good yields with 83–94% *ee* (Scheme 1).[3]



Scheme 1. Chromium(III)-catalyzed enantioselective aziridine opening with trimethylsilyl azide developed by Jacobsen and co-workers.[3] MS = molecular sieves, TMS = trimethylsilyl.

Shibasaki and co-workers achieved a breakthrough in 2005 with the development of a catalyst prepared in situ from $Gd(OiPr)_3$ and the chiral ligand **5** derived from glucose. A similar ligand had been used successfully by the same research group in the asymmetric Strecker reaction of ketimines.[4] Now *meso* *N*-4-nitrobenzoylaziridines such as **4** were opened with trimethylsilyl cyanide in high yields with good to very good selectivities to provide 1,2-amidonitriles such as **6**, which are valuable precursors to β-amino acids (Scheme 2).[5]



Scheme 2. Gadolinium-catalyzed enantioselective aziridine opening with trimethylsilyl cyanide developed by Shibasaki and co-workers.[5,6] TFA = trifluoroacetic acid.

The enantioselectivity of the reaction could be increased further by modification of the structure of the chiral ligand: With only 2 mol% of the catalyst prepared from $Gd(OiPr)_3$ and the chiral ligand **7** (in the ratio 1:2), the reaction products were obtained in almost quantitative yields with up to 99% *ee*; interestingly, the opposite enantiomers were obtained.[6] The smaller distance between the phosphine oxide unit and the neighboring hydroxy group in **7** apparently leads to such a change in the binding mode of the gadolinium ligand that asymmetric induction in the reaction is completely reversed.

ESIMS investigations of the catalyst mixture derived from $Gd(OiPr)_3$ and the ligand **5** led to the conclusion that the reaction proceeds by a mechanism involving a dimetal species (Scheme 3). Thus, a 2:3 metal/ligand complex **8** is formed initially and then converted into the active, protodesilylated catalyst **9** with excess ligand, or better still with the additive 2,6-dimethylphenol. A catalytic amount of trifluoroacetic acid stabilizes the binuclear Gd complex by bridging the two metal centers. The binding mode of the ligand **5** was also derived from crystal structures of the related lanthanum–ligand cluster.[7] According to this study, **5** behaves as a tetracoordinating ligand but binds to at least two metal atoms at the same time.

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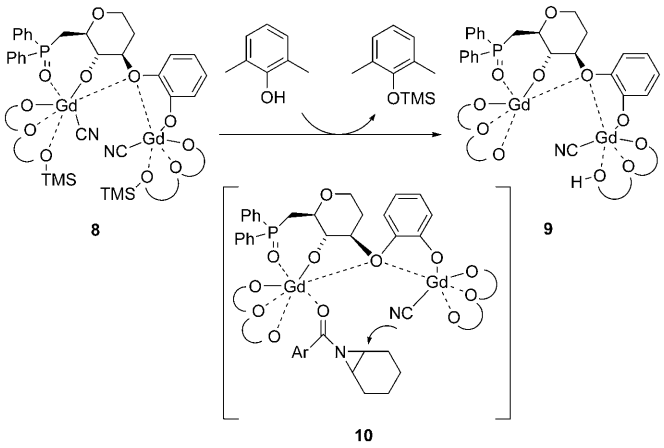
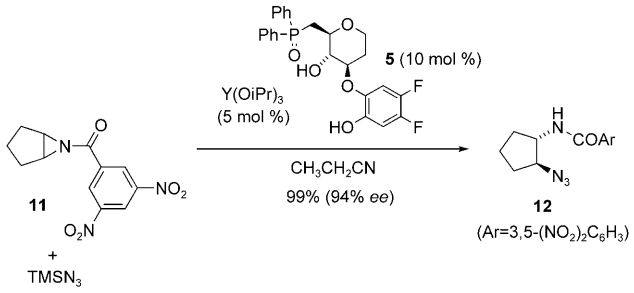


Scheme 3. Postulated mechanism of the gadolinium-catalyzed aziridine opening developed by Shibasaki and co-workers.[5,6]

Kinetic investigations[4] of the addition of cyanide to ketimines under the catalysis of the same metal complex showed that the reaction rate is independent of the concentration of trimethylsilyl cyanide, which suggests that a gadolinium cyanide generated in situ, as in **9**, is the reactive nucleophile. On this basis, a mechanism involving cooperative catalysis by both metal centers in the complex **10** was postulated for the aziridine opening, whereby one metal center acts as a Lewis acid to activate the aziridine, and the other directs the addition of the nucleophile to the substrate in an intramolecular and highly selective fashion (Scheme 3).

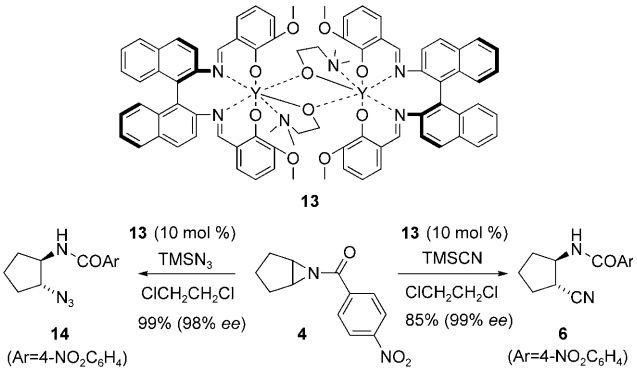
Cooperative, asymmetric bimetallic catalysis has established itself as a general catalysis principle in organic chemistry.[8] In particular, Shibasaki and co-workers have used this principle in a broad range of C–C coupling reactions, typically with lanthanoid–alkali metal binaphtholate complexes.[9] Nugent and Finn were able to show that the zirconium/(*S*,*S*,*S*)-triisopropanolamine-catalyzed enantioselective ring opening of *meso* epoxides with trimethylsilyl azide also proceeds by a bimetallic mechanism.[10] The epoxide-opening reactions of Jacobsen and co-workers catalyzed by chromium(III)–*N*,*N*′-bis(salicylidene)cyclohexanediamine (salen) complexes also use this principle, although not in an intramolecular but in an intermolecular sense.[11] Further examples of this principle can be found in a review article on this topic.[8b]

With the metal alkoxide $Y(OiPr)_3$ instead of $Gd(OiPr)_3$, Shibasaki and co-workers developed a highly enantioselective azidolysis of *meso* aziridines such as **11** (again with the chiral ligand **5**) to give 1,2-azidoamides such as **12** in high yields with up to 96% *ee* (Scheme 4).[12] A broad range of cyclic, acyclic, and heterocyclic *meso* aziridines could be ring-opened very selectively by this method. Since the absolute configuration of the products is the same as for the Gd-catalyzed reaction with trimethylsilyl cyanide, it seems reasonable to assume that in this case, too, the bimetallic mechanism described above is active. To demonstrate the synthetic potential of the 1,2-azidoamides formed, one of the products was transformed into the antiviral compound tamiflu in a multistep sequence.



Scheme 4. Yttrium-catalyzed enantioselective aziridine ring opening with trimethylsilyl azide developed by Shibasaki and co-workers.[12]

Recently, RajanBabu and co-workers carried out a highly enantioselective ring opening of *meso* *N*-4-nitrobenzoylaziridines such as **4** with trimethylsilyl cyanide and trimethylsilyl azide under the catalysis of the dimeric yttrium complex **13** (10 mol%), which has been fully characterized crystallographically (Scheme 5).[13] The complex **13** is accessible by the



Scheme 5. Enantioselective aziridine opening with trimethylsilyl azide and trimethylsilyl cyanide catalyzed by the dimeric yttrium complex **13** developed by RajanBabu and co-workers.[13]

treatment of $Y(OCH_2CH_2NMe_2)_3$ with the corresponding chiral binaphthalenediamine–salen ligand and careful recrystallization. 1,2-Amidonitriles such as **6** and 1,2-azidoamides such as **14** were obtained with excellent enantioselectivities (up to 99% *ee*) that surpass the best selectivities previously observed. The corresponding monomeric yttrium complex, formed from $Y[N(SiHMe_2)_2]_3$ and the same chiral ligand, also catalyzed the reaction; however, the products were formed with 55% *ee* at the most.

The crystal structure of the dimeric, C_2-symmetric complex **13** shows that the lower side is shielded by the methoxy and dimethylamino units, whereas the binaphthyl backbone of the chiral ligand essentially blocks the upper side of the complex (Figure 1). The actual structure in solution, and above all in the presence of the aziridine and the nucleophile, will differ from the structure in Figure 1, as free coordination sites must be made available at the metal centers for the binding of the substrate.

The fact that the monomeric yttrium complex catalyzes the ring opening with only moderate enantioselectively

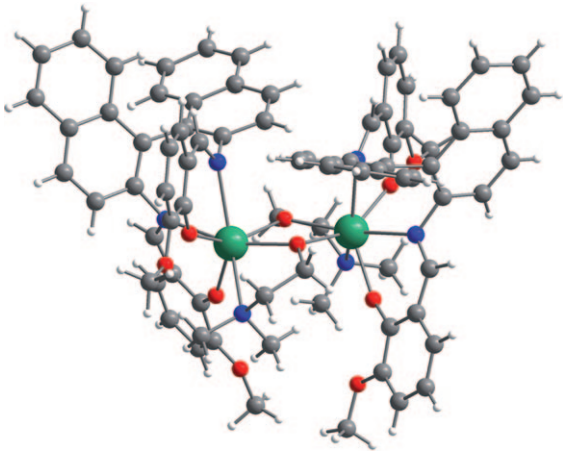
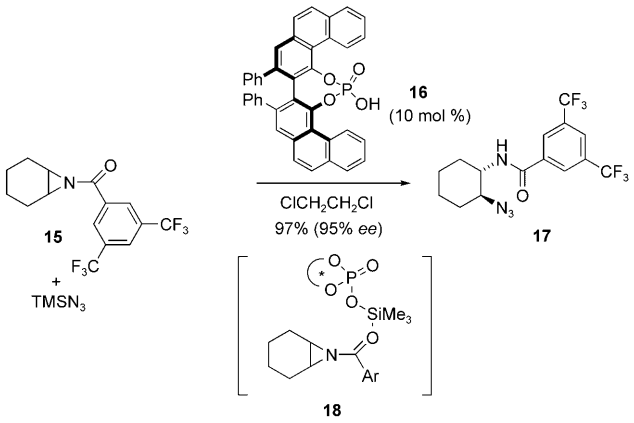


Figure 1. Structure of the dimeric yttrium complex **13** in the crystal according to RajanBabu and co-workers.[13] Gray C, white H, blue N, red O, green Y.



Scheme 6. Brønsted acid catalyzed aziridine opening with trimethylsilyl azide developed by Antilla and co-workers.[15]

suggests that with this catalyst too, a cooperative interaction of the two yttrium centers occurs in the catalytic cycle. Moreover, IR spectroscopic monitoring of the reaction of a structurally similar yttrium complex with an equimolar amount of trimethylsilyl cyanide showed a very rapid and quantitative cyanide transfer from the silicon atom to the yttrium complex.[14] Together with the crystal-structure analysis, this finding suggests, quite within the sense of the model proposed by Nugent and Finn,[10] that in **13** one yttrium atom activates the *N*-acyl aziridine as a Lewis acid, whereas the second yttrium atom activates the cyanide or the azide nucleophile and transfers it in an intramolecular fashion to the aziridine.

Antilla and co-workers demonstrated in 2007 that not only metal complexes can be effective chiral catalysts for the asymmetric ring opening of *meso* aziridines.[15] With the aid of the (*S*)-vapol phosphoric acid **16** ((*S*)-vapol = (*S*)-2,2′-diphenyl-[3,3′-biphenanthrene]-4,4′-diol), *meso* *N*-3,5-bis(trifluoromethyl)benzoylaziridines such as **15** could be opened with trimethylsilyl azide to give 1,2-azidoamides such as **17** in good yields with up to 95% *ee* (Scheme 6). On the basis of NMR spectroscopic investigations, it was postulated that a phosphoric acid silyl ester is formed in situ and transformed into a Lewis acid–base adduct **18** with the acyl aziridine, which is then opened by the HN_3 nucleophile.

In summary, a number of highly selective catalytic methods developed in recent years for the asymmetric ring opening of *meso* aziridines make valuable 1,2-difunctionalized fine chemicals accessible in high enantiomeric purity. However, in spite of these impressive advances, there is still a need for broadly applicable, practical methods with even more readily accessible and more manageable catalysts, and ideally methods that are not restricted to silyl nucleophiles[16].

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