154. Reactions of Diazo Compounds with Imines

Preliminary Communication

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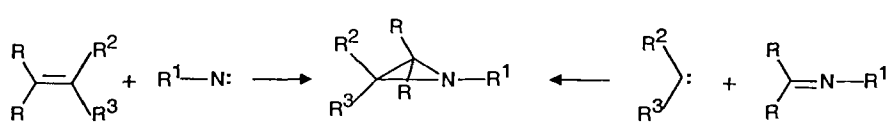
The $[Rh_2(OAc)_4]$-catalyzed addition of methyl diazoacetate to *N*-benzylideneaniline (**1a**) afforded the imine *cis*-**2** in 35% yield. Under catalysis by chiral Rh^{II} catalysts, however, only racemic **1a** was produced, and the yield was low. In the presence of dimethyl maleate, aziridine formation was suppressed, and an intermediate ylide **6** was trapped as cycloadduct **7**. No aziridines were obtained, however, from **1b**, **1c**, and **3**. The iminium salt **8** reacted with (trimethylsilyl)diazomethane in the absence of $[Rh_2(OAc)_4]$ *via* dipolar cycloaddition followed by extrusion of N_2 to **10**.

Aziridines are attractive intermediates in organic synthesis, and a variety of approaches to their synthesis have been investigated [1]. The most direct access to aziridines consists of nitrene addition to olefins [2] (*Scheme 1*). Systems for aziridination of olefins in the presence of chiral transition-metal catalysts have been reported from several laboratories [3–5]. The decomposition of PhI=NTs by transition metals, first described by *Mansuy* and coworkers [3], has been successfully developed into a system for asymmetric aziridination by the groups of *Evans et al.* [6] and *Jacobsen* and coworkers [7] using chiral Cu catalysts. Aziridines are formed in high yield and with high enantiomeric excess. An alternative approach for catalytic generation of aziridines, consisting of carbene addition to imines, has been investigated in the past with limited success [8–10], and the general idea was that this was not a viable route to aziridines.

Scheme 1

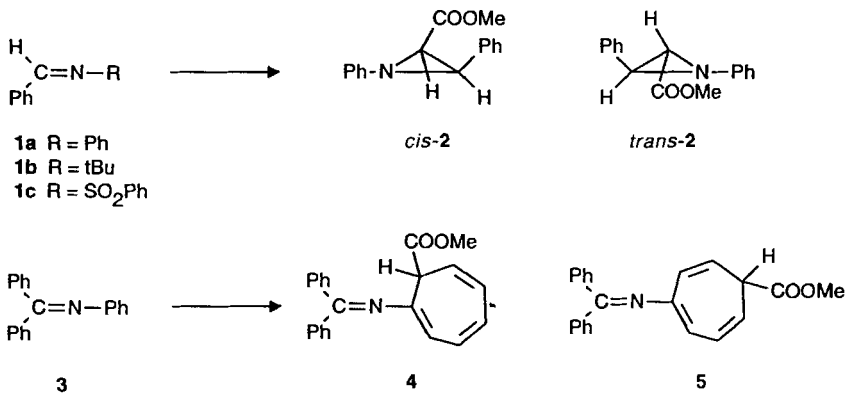


Very recently, however, the *Jacobsen* group reported on the reactions between imines and ethyl diazoacetates in the presence of chiral Cu^{I}-bis(dihydrooxazole) complexes [11]. Aziridines were produced in moderate yields (10–37%; 65% with an achiral bis(dihydrooxazole)) with ee's reaching 67%. A mechanism involving an intermediate achiral ylide, weakly associated with the catalyst, was proposed to explain the low enantioselectivity of the carbene transfer. Asymmetric Rh-based cyclopropanation systems were also tried, but were found less satisfactory than those containing Cu. Subsequently, *Rasmussen* and

Jørgensen reported aziridine yields of 80–90% upon addition of diazoacetates to selected imines at −25° under catalysis with $Cu(OTf)_2$ [12]. Yields dropped to 50–60%, however, when a chiral bis(dihydrooxazole) ligand was used, and the enantioselectivity, again, was low. These events prompted us to disclose our own findings on reactions of imines with diazo compounds in the presence and absence of Rh^{II} catalysts.

When methyl diazoacetate was decomposed in the presence of a four-fold excess of *N*-benzylideneaniline (**1a**) and $[Rh_2(OAc)_4]$ (1%) in CH_2Cl_2 the aziridine *cis*-**2** was formed in 35% yield (*Scheme 2*). The *trans*-isomer was not detected in the reaction mixture. With **3**, the attack occurred mainly at the benzene ring of the aniline moiety, affording the isomeric cycloheptatrienes **4** and **5** in yields of 5 and 30%, respectively. The structure of **4** was deduced from the ^{1}H-NMR, which revealed a *doublet* (J = 7.0 Hz) for H–C(7) at 3.24 ppm. The structure of **5** follows equally from the pattern of the olefinic protons, in particular from the *ABX* system for H–C(2), H–C(1), and H–C(7). It was definitively established by X-ray crystal-structure analysis[1]). The seven-membered ring of **5** adopts a boat conformation with a pseudo-mirror plane passing through C(7).

Scheme 2



Trace amounts of aziridine *cis*-**2** were formed upon replacement of $[Rh_2(OAc)_4]$ by $[Rh_2(pfb)_4]$ (dirhodium tetrakis(perfluorobutyrate)) [13]. When $[Rh_2(OAc)_4]$ was replaced with a chiral Rh^{II} catalyst, $[Rh_2\{(2S)\text{-mepy}\}_4]$ [14] or $[Rh_2\{(S)\text{-ptpa}\}_4]$ [15], the yields of *cis*-**2** dropped dramatically to *ca.* 5%. The aziridine produced from $[Rh_2\{(2S)\text{-mepy}\}_4]$ consisted of a 2:1 *cis*/*trans*-mixture, while with $[Rh_2(ptpa)_4]$ only the *cis*-isomer was formed. The *trans*-isomer obtained from **1** with $[Rh_2\{(2S)\text{-mepy}\}_4]$ was not isolated, but was identified by comparison of the ^{1}H-NMR data of the *cis*/*trans*-mixture with those reported in [16]. Most significantly, the aziridines obtained with the chiral catalysts were racemic.

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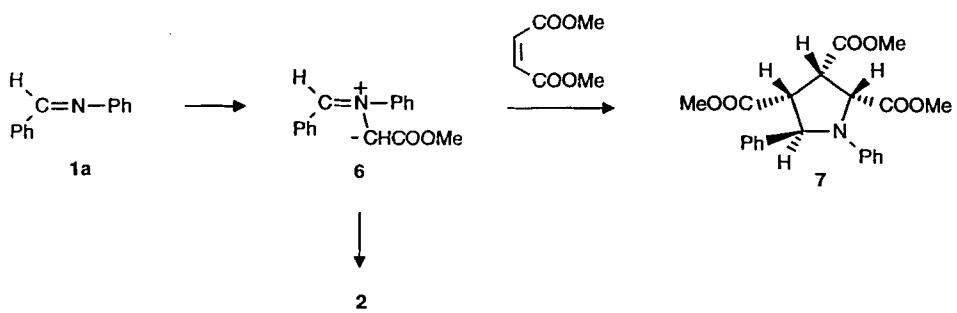
[1]) Crystallographic data have been deposited with the *Cambridge Crystallographic Data Centre*, University Chemical Laboratory, 12 Union Road, Cambridge, CB2 1EZ, England.

Cyclopropanation may proceed by direct attack of the carbene to the imine C=N bond, or *via* an intermediate ylide **6** which cyclizes in a subsequent step (*Scheme 3*). In the latter case, asymmetric induction is only expected, if the ylide is coordinated to the chiral catalyst, since the free ylide is achiral because of its planar structure. The traditional test for ylide intermediates consists of their trapping with dipolarophiles [17]. Although it was originally believed that the Cu-catalyzed cyclopropanation of imines proceeded by direct attack on the C=N bond [18], the intermediacy of ylides in these reactions was established more than ten years ago by their trapping with dimethyl maleate and benzaldehyde [19], and was recently confirmed by *Jacobsen* and coworkers [11]. Accordingly, the aziridination of **1a** with $[Rh_2(OAc)_4]$ was repeated in the presence of dimethyl maleate. The *cis*-configurated pyrrolidine **7** was isolated in 24% yield, while aziridine formation was entirely suppressed. The relative configuration of **7** was assigned on the grounds of ^{1}H-NMR coupling constants and NOESY experiments. H–C(2) showed a strong interaction with the protons of the Ph substituent at C(5), indicating *trans*-configuration for the substituents at C(2) and C(5). All H-atoms in α-position to the COOMe groups (at C(2), C(3), C(4)) exhibited strong mutual interactions in the NOESY spectrum, while the H-atom adjacent to the Ph substituent at C(5) interacted only very weakly with the others.

These observations with the Rh^{II}-catalyzed cyclopropanation of imines are consistent with the mechanism proposed by *Jacobsen* and coworkers [11] for the analogous Cu-catalyzed imine cyclopropanation. In both systems, the carbene associates first with the lone pair of the imine to form an ylide which cyclizes subsequently to the aziridine. The ylide is achiral. However, in the case of Cu catalysts, it remains associated with the catalyst, so that a limited degree of asymmetric induction may still be achieved. This appears not to be the case in the cyclopropanation with Rh^{II}, where it must be fully separated from the catalyst so that there is no asymmetric induction.

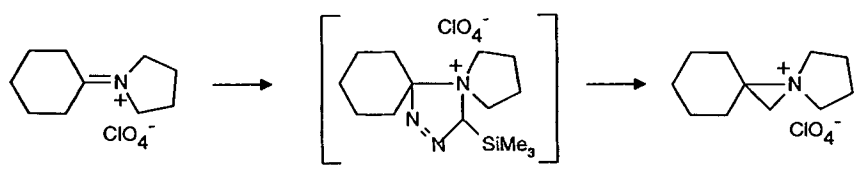
Scheme 3



Experiments directed to circumvent ylide formation in the cyclopropanation of C=N bonds have been unsuccessful to date. Replacement of the Ph by a *t*-Bu group in the imine was expected to exert some steric hindrance around the lone pair of the N-atom. However, *N*-benzylidene(*tert*-butyl)amine (**1b**) was found entirely unreactive towards cyclopropanation with methyl diazoacetate/$[Rh_2(OAc)_4]$. Only carbene dimers (dimethyl

fumarate and dimethyl maleate) as well as unreacted **1b** and its hydrolysis products were recovered. Similarly, *N*-benzylidenebenzenesulfonamide (**1c**) was exposed to methyl diazoacetate/$[Rh_2(OAc)_4]$ at 25, 60, and 110° in the expectation that the electron-withdrawing sulfonyl group would decrease the tendency of ylide formation in **1c**. However, the reaction afforded no aziridines, and only carbene dimers, unreacted **1c**, or its decomposition products were observed. No ylide was intercepted, when the reaction was carried out in the presence of dimethyl fumarate (110°). The iminium salt **8** which has no lone pair available for ylide formation was unreactive towards diazoacetate in the presence of $[Rh_2(OAc)_4]$. No reaction occurred with the less electrophilic metallocarbene generated from $Me_3SiCHN_2/[Rh_2(OAc)_4]$. However, Me_3SiCHN_2 alone reacted with **8** in analogy to CH_2N_2 [20] in 48 h at 25° to the known aziridinium salt **10** (*Scheme 4*). Since diazo decomposition with $[Rh_2(OAc)_4]$ is a very fast process, this suggests that cyclopropanation of **8** does not occur *via* a metallocarbene, but rather by cycloaddition of the diazo compound to an iminium salt **9** which suffers N_2 extrusion and spontaneous loss of the Me_3Si group to afford **10**.

Scheme 4



Our results, combined with those of *Jacobsen* and coworkers [11] indicate that the Rh^{II}-catalyzed diazo decomposition in the presence of imines is less promising than the Cu-catalyzed variant for preparation of chiral aziridines. Although ylide formation between metallocarbene and imine does not entirely preclude asymmetric induction, the enantioselectivity is lower in the Cu-catalyzed aziridination than in the analogous carbene addition to C=C bond, and it disappears totally in the Rh^{II}-catalyzed reactions. Apparently, the ylide-coordinating capacity of the Rh^{II} catalyst is insufficient to prevent diffusion of the ylide away from the chiral environment, so that no asymmetric induction results.

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