First osmium-catalysed ketamination of alkenes†

Amparo Villar,[a] Claas H. Hövelmann,[a] Martin Nieger[b] and Kilian Muñiz*[a]

Received (in Cambridge, UK) 14th April 2005, Accepted 16th May 2005
First published as an Advance Article on the web 1st June 2005
DOI: 10.1039/b505278p

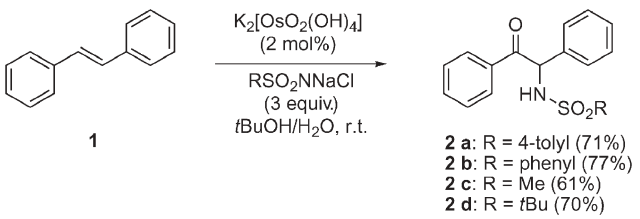
Conditions for a first oxidative conversion of alkenes into 2-amino ketones are described, which yield racemic products within a direct oxidation pathway and 2-amino ketones with up to 99% enantiomeric excess from the corresponding enantiopure amino alcohols.

The functional entity of the 2-amino ketone represents an important building block for the synthesis of higher functionalised organic molecules. It is present in biologically relevant natural products such as the proteasome inhibitor epoxomicin,[1] the antitumor agent eponemycin[1] and mersingins A and B.[2] In spite of their structural importance, direct synthetic access to 2-amino ketones is rather rare. In principle, a direct conversion of alkenes into 2-amino ketones would be a useful contribution to the synthesis of this functional class. Current general synthetic approaches rely on amino acid transformation,[3] C–C or C–N bond formation[4,5] or enol ether oxidation.[6]

A complimentary process is described herein which consists of an osmium-catalysed formation of 2-amino ketones from alkenes.

Usually, alkenes are transformed into vicinal diols or amino alcohols, respectively, employing catalytic amounts of an osmium(VIII) complex such as OsO_4 or monomeric imido derivatives thereof.[7,8] These oxidation reactions usually benefit from a remarkable selectivity since other products can only be obtained upon significant alteration of the reaction conditions.[9]

An initial investigation on the general course of osmium-catalysed aminohydroxylation of (*E*)-stilbene **1** with chloramine-T yielded varying amounts of an amino ketone. Subsequent optimisation led to the development of a protocol, which did no longer provide any detectable amount of amino alcohol, but rather yielded the respective amino ketone **2a** as the major product (71% isolated yield, Scheme 1), together with minor amounts of benzil (14–35%), which is assumed to originate from additional oxidation. The exact course of formation is currently under investigation.[10] An X-ray determination confirmed the overall constitution of the major product (Fig. 1).‡ The most important difference from the standard Sharpless AA procedure[8,11] consists in the absence of a chiral cinchona alkaloid ligand. Under such modification, the reaction proved general for a variety of sulfonamide-based nitrenes promoting formation of the corresponding amino ketones in good yields of 61–77% (Scheme 1). Amino ketone formation was also accomplished for other alkenes. For example, 5-decene **3** gave the corresponding amino ketone **4** in 82% yield (Scheme 2). Generally, the inherent problem of regioselectivity in the initial aminohydroxylation step plays a decisive role, as styrene and β-methyl styrene yielded the expected *N*-tosyl-1-phenyl-2-amino ketones **6a** and **6b** in 51% and 42% yield, respectively. Due to apparent preferential reactivity of benzylic C–X moieties, the regioisomeric intermediate amino alcohols underwent complete overoxidation to dicarbonyls and degradation products thereof. Since the initial aminohydroxylation



Scheme 1 Direct ketamination of stilbene.

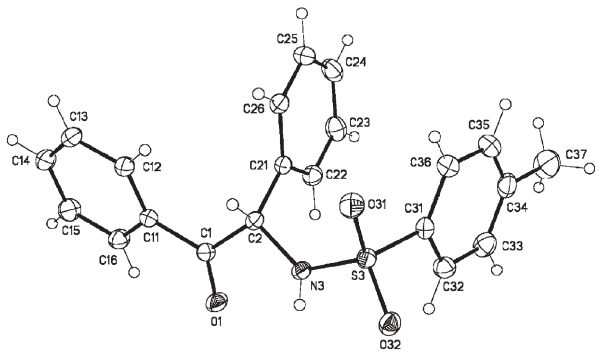
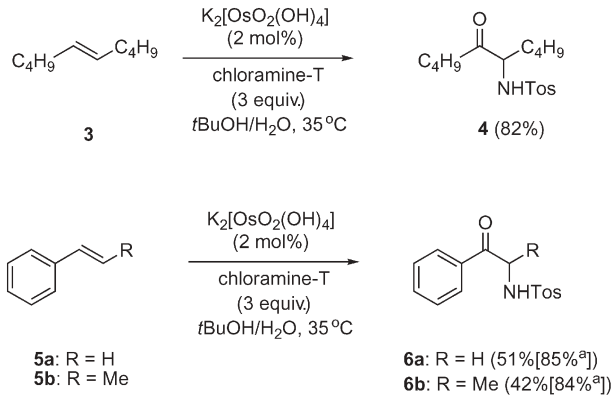


Fig. 1 Solid state structure of 2-amino ketone **2a**.† Selected bond lengths (Å) and angles (°): O(1)–C(1) 1.2136 (14), C(2)–N(3) 1.4593(14), N(3)–C(2)–C(1) 106.18(9), O(1)–C(1)–C(2) 119.90(10).



Scheme 2 Direct ketamination of (*E*)-5-decene and styrenes. [a]Based on maximum yield for major regioisomer.

† Electronic supplementary information (ESI) available: characterisation of reaction products and spectral characterisation for new compounds. See http://www.rsc.org/suppdata/cc/b5/b505278p/index.sht

*kilian.muniz@uni-bonn.de

of **5a** and **5b** had been known to provide regioselectivities of 1.5:1 and 1:1, respectively,[12] maximum yields of 60 and 50% are possible for the synthesis of amino ketones **6a** and **6b**.

Such an excess formation of 2-amino ketones from olefin oxidation is without precedence. More importantly, it relies on the same oxidant as the parent aminohydroxylation.[8] This is in noteworthy contrast to the overoxidation in related dihydroxylation reactions to form hydroxy ketones which had been encountered in early protocols and required harsh oxidants such as *tert*-butyl hydroperoxide or hydrogen peroxide.[13,14]

The mechanistic rationale of this new Os-catalysed reaction is given in Fig. 2 and characterises the direct amino ketone formation as an alternative pathway within the established secondary cycle of aminohydroxylation.[8] After initial aminohydroxylation of the alkene, the resulting osma(VI)azaglycolate **A** is re-oxidised to osma(VIII)azaglycolate **B**. In the absence of any cinchona alkaloid ligand, hydrolysis of the amino alcohol is slow, leading to concomitant oxidation of a second alkene to furnish bis(azaglycolate) **C**, and upon further re-oxidation, osma(VIII)-bis(azaglycolate) **D**. Intramolecular oxidation of one amino alcohol ligand as depicted, forms the mono-bound 2-amino ketone (intermediate **E**), which is hydrolysed off to regenerate complex **A** and close the overall catalytic cycle.

Upon addition of a cinchona alkaloid ligand to the reaction mixture, amino alcohols become the major products as known from the seminal publications by Sharpless.[11] This is readily explained by the enhanced hydrolysis rate of the intermediate osma(VI)azaglycolate **B** under such conditions.[8,11] Clearly, the absence of the ligand is crucial for the overall ketamination course.[15–17]

As a further consequence of these mechanistic considerations, an oxidative process from isolated amino alcohols was envisioned within the same catalytic cycle (Fig. 3). At the end of the reaction, the original ketamination cycle is interrupted at the stage of **B** due to the absence of olefin. Hence, condensation with free amino alcohol can take place to give **D** directly. In the presence of catalytic amounts of osmium and in the absence of any additional ligand, amino alcohols should thus be oxidised to amino ketones *via* continuous regeneration of **D**. Therefore, this sequence

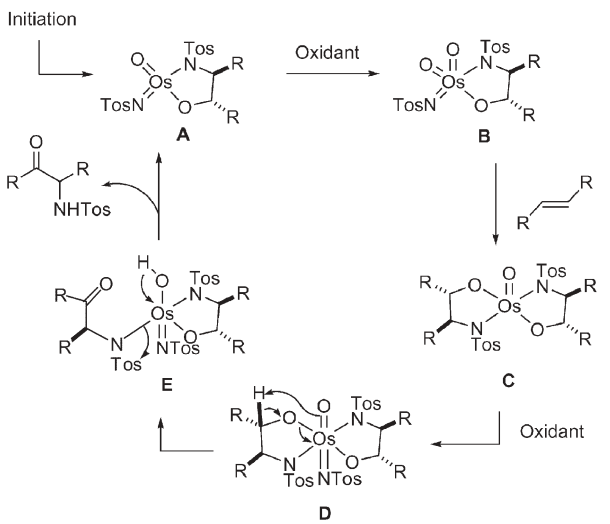


Fig. 2 Catalytic pathways for direct ketamination of alkenes.

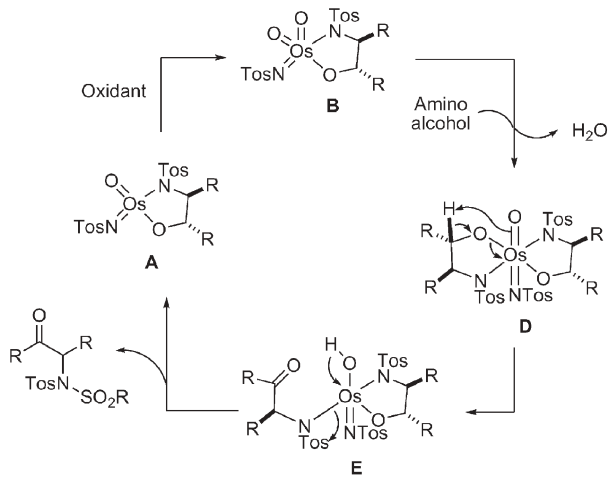
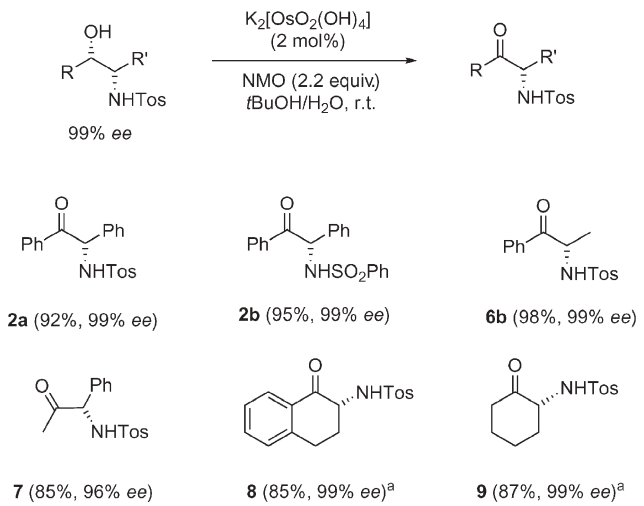


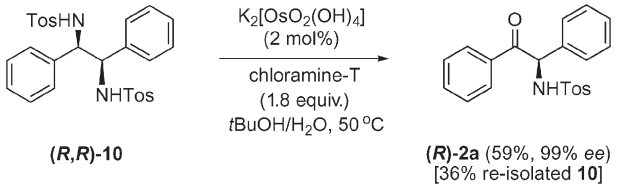
Fig. 3 Catalytic cycle for oxidation of amino alcohols.

represents the correction process for direct ketamination since minor amounts of liberated amino alcohol are subsequently oxidised to amino ketones. This explains the absence of any detectable amount of amino alcohol under the conditions for direct ketamination. Moreover, 2-amino ketones should be accessible independently from oxidation of amino alcohols through the catalytic cycle depicted in Fig. 3.

In fact, 1,2-diphenyl-2-tosylaminoethanol was cleanly converted to **2a** in the presence of 2 mol% potassium osmate and 2.2 equivalents of chloramine-T. Similarly, 2-tosylaminoacetophenone **6a** and 2-methyl-2-tosylaminopropiophenone were obtained from oxidation of the respective achiral amino alcohols. More importantly, catalysis within the cycle of Fig. 3 allows for the use of oxygen-based oxidants. Among screened oxidants were *N*-methyl morpholine *N*-oxide (NMO), trimethylamine *N*-oxide and *tert*-butyl hydroperoxide. Here, NMO performed best and, unlike chloramine-T, allowed for an epimerisation-free conversion to yield enantiopure 2-amino ketones from enantiopure vicinal amino alcohols. Under optimised conditions, (*S*)-configured amino ketones **2a**, **2b**, **6b** and **7** were obtained from the respective (*S*,*S*)-amino alcohols (Scheme 3). These were derived from the



Scheme 3 Synthesis of enantiomerically enriched 2-amino ketones. [a]From the corresponding *trans*-configured amino alcohol.



Scheme 4 Synthesis of enantiopure 2-amino ketone **2a** from diamine **10**.

standard AA reaction[11] followed by enantiomeric enrichment through crystallisation (99% ee). In an analogous manner, (*R*,*R*)-1,2-diphenyl-2-tosylaminoethanol gave (*R*)-**2a** in 99% ee. In addition, NMO proved an optimum oxidant regarding the chemoselectivity within the final oxidation. Thus, within the competing ketone *vs.* imine oxidation at the stage of the intermediate **D**, no benzil formation was detected in the formation of **2a** or **2b** and the compounds **6b** and **7** were equally formed with complete chemoselectivity and in high yields.

Enantiopure 2-amino ketones **8**, **9** were obtained from *trans*-configured amino alcohol precursors. These results demonstrate the high efficiency of the present process since the NMO-based reaction in Scheme 3 leads to high chemoselectivity in the oxidation of the amino alcohols, generally without any detectable degree of racemisation or overoxidation

Interestingly, the reaction was also found to proceed with a vicinal diamine. Application of symmetrically bis-tosylated (*R*,*R*)-ethylenediamine **10** led to enantiomerically pure (*R*)-**2a**. The reaction was significantly slower than for related amino alcohols and was carried out at 50 °C (Scheme 4), yielding 59% of **2a** after a period of 48 h. This result agrees well with the observation from ketamination reactions which showed a kinetic oxidation preference for alcohol over tosylamido groups and thereby supports the mechanistic hypothesis outlined in Figs. 2 and 3.

To summarise, we have described a new osmium-catalysed oxidation of alkenes, which yields 2-amino ketones from alkenes under mild conditions. The reaction can either be carried out as a direct ketamination or, alternatively, as a sequential process which consists of asymmetric aminohydroxylation and subsequent oxidation. The latter variant conveniently leads to enantiopure 2-amino ketones.

The overall development of the reaction represents the first successful alteration of an established osmium catalytic protocol toward alternative product formation. We expect future investigation of imido osmium compounds and catalysts to devise further new reactivity in this area.

The present work was generously supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie within the VCI. The authors thank Prof. Dr K. H. Dötz for his support, and A. V. is grateful to the Spanish Ministerio de Educación y Ciencia for a visiting fellowship.

Amparo Villar,[a] Claas H. Hövelmann,[a] Martin Nieger[b] and Kilian Muñiz*[a]
[a]*Kekulé-Institut für Organische Chemie und Biochemie, Gerhard-Domagk-Str. 1, D-53121 Bonn, Germany. E-mail: kilian.muniz@uni-bonn.de; Fax: +49 228 735813; Tel: +49 228 736553*
[b]*Institut für Anorganische Chemie, Gerhard-Domagk-Str. 1, D-53121 Bonn, Germany. E-mail: nieger@joyx.joensuu.fi*

Notes and references

‡ Data for crystal structure analysis were measured on a Nonius KappaCCD diffractometer. **2a**: $C_{21}H_{19}NO_3S$ monoclinic, $P2_1/n$ (No. 14), a = 12.6115(1), b = 5.9741(1), c = 24.2313(2) Å, β = 101.681(1)°, V = 1787.83(4) Å^3, Z = 4, T = 123 K, μ(MoKα) = 0.202 mm^{-1}, 32585 reflections, 4091 unique reflections ($2\theta_{max}$ = 50°), R_1 = 0.0320 [$I > 2\sigma(I)$], wR_2 = 0.0906 (all data), 239 parameters and 1 restraint. Empirical absorption correction was applied. CCDC 268052. See http://www.rsc.org/suppdata/cc/b5/b505278p/index.sht for crystallographic data in CIF or other electronic format.

1 M. Hanada, K. Sugawara, K. Koko, S. Toda, Y. Nishiyama, K. Tomita, H. Yamamoto, M. Konishi and T. Oki, *J. Antibiot.*, 1992, **45**, 1746; L. Meng, R. Mohan, B. H. B. Kwok, M. Elofsson, N. Sin and C. M. Crews, *Proc. Natl. Acad. Sci. U. S. A.*, 1999, **96**, 10403.
2 K. Yoganathan, W.-H. Wong and T.-S. Kam, *Nat. Prod. Lett.*, 1995, **5**, 309.
3 (*a*) M. T. Reetz, *Chem. Rev.*, 1999, **99**, 1121; (*b*) L. De Luca, G. Giacomelli and A. Porcheddu, *Org. Lett.*, 2001, **3**, 1519.
4 K. W. Kells and J. M. Chong, *J. Am. Chem. Soc.*, 2004, **126**, 15666; A. E. Mattson and K. A. Scheidt, *Org. Lett.*, 2004, **6**, 4363; J. A. Murry, D. E. Frantz, A. Soheili, R. Tillyer, E. J. J. Grabowski and P. J. Reider, *J. Am. Chem. Soc.*, 2001, **123**, 9696.
5 D. Enders, C. Poiesz and R. Joseph, *Tetrahedron: Asymmetry*, 1998, **9**, 3709; N. Kumaragurubaran, K. Juhl, W. Zhuang, A. Bøgevig and K. A. Jørgensen, *J. Am. Chem. Soc.*, 2002, **124**, 6254; N. Momiyama and H. Yamamoto, *J. Am. Chem. Soc.*, 2003, **125**, 6038; N. Momiyama, H. Torii, S. Saito and H. Yamamoto, *Proc. Natl. Acad. Sci. U. S. A.*, 2004, **101**, 5374; R. O. Duthaler, *Angew. Chem. Int. Ed.*, 2003, **42**, 975.
6 D. A. Evans and D. S. Johnson, *Org. Lett.*, 1999, **1**, 595; S. Minakata, T. Ando, M. Nishimura, I. Ryu and M. Komatsu, *Angew. Chem. Int. Ed.*, 1998, **37**, 3392; D. A. Evans, M. T. Bildodean and M. M. Faul, *J. Am. Chem. Soc.*, 1994, **116**, 2742.
7 H. C. Kolb, M. S. VanNieuwenhze and K. B. Sharpless, *Chem. Rev.*, 1994, **94**, 2483.
8 K. Muñiz, *Chem. Soc. Rev.*, 2004, **33**, 160.
9 C. Döbler, G. Mehltretter, U. Sundermeier and M. Beller, *J. Organomet. Chem.*, 2001, **621**, 70; B. R. Travis, R. S. Narayan and B. Borhan, *J. Am. Chem. Soc.*, 2002, **124**, 3824; W. Yu, Y. Mei, Y. Kang, Z. Hua and Z. Jin, *Org. Lett.*, 2004, **6**, 3217; X. Qi, S.-H. Lee, J. Y. Kwon, S.-J. Kim, Y. Kim, Y.-S. Lee and J. Yoon, *J. Org. Chem.*, 2003, **68**, 9140.
10 For an example of a different overoxidation in a related carbamate-based aminohydroxylation: Z. Liu, N. Ma, Y. Jia, M. Bois-Choussy, A. Malabarba and J. Zhu, *J. Org. Chem.*, 2005, **70**, 2847.
11 G. Li, H.-T. Chang and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 451; J. Rudolph, P. C. Sennhenn, C. P. Vlaar and K. B. Sharpless, *Angew. Chem., Int. Ed. Engl.*, 1996, **35**, 2813.
12 K. B. Sharpless, A. O. Chong and K. Oshima, *J. Org. Chem.*, 1976, **41**, 177.
13 K. B. Sharpless and K. Akashi, *J. Am. Chem. Soc.*, 1976, **98**, 1986; S.-I. Murahashi, T. Naota and H. Hanaoka, *Chem. Lett.*, 1993, 1767.
14 An alternative synthesis of 2-amino ketones through Os-catalysed aminohydroxylation of silyl enol ethers was reported previously: P. Phukan, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2003, **42**, 921; P. Phukan and A. Sudalai, *Tetrahedron: Asymmetry*, 1998, **9**, 1001.
15 The kinetic stability of the bis(azaglycolate)s **C** and **D** is decisive. It is based on the singular character of the sulfonyl moiety. Alternative substituents, as obtained from carbamate- and acetamide-based nitrenoids, lead to enhanced hydrolysis and therefore to diminished formation of amino ketones.
16 For a related mechanistic study on undesired formation of 2-hydroxy ketones under OsO_4-catalysis, see: B. B. Lohray, V. Bhushan and R. K. Kumar, *J. Org. Chem.*, 1994, **59**, 1375.
17 Recent work by Plietker has introduced a ruthenium-catalysed ketohydroxylation of olefins. Interestingly, the postulated catalytic cycles differ substantially from those of our Os-catalysis: B. Plietker and M. Niggemann, *Org. Biomol. Chem.*, 2004, 2403; B. Plietker, *J. Org. Chem.*, 2004, **69**, 8287; B. Plietker, *Eur. J. Org. Chem.*, 2005, 1919.