ORGANIC LETTERS

2008
Vol. 10, No. 13
2805−2807

Homoallyllic Nitrone Isomerization: Convenient Enantioselective Synthesis of Homoallylic Nitrones and Homoallylic Hydroxylamines

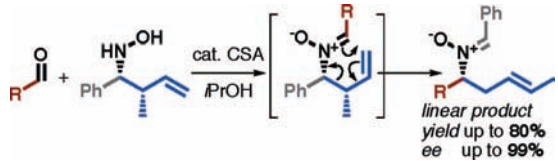
Hin-Soon Cheng, Ai-Hua Seow, and Teck-Peng Loh*

Division of Chemistry and Biological Chemistry, School of Physical and Mathematical Sciences, Nanyang Technological University, Singapore 637616

teckpeng@ntu.edu.sg

Received April 22, 2008

ABSTRACT



An α-regioselective synthesis of homoallylic nitrones from aldehydes is reported on the basis of [3,3]-sigmatropic rearrangement. The products are obtained in up to 99% enantioselectivity and up to 80% yield under environmentally benign and mild reaction conditions.

Homoallylic amines are versatile synthons in synthetic chemistry since the allyl group can be readily converted into a wide variety of synthetically useful compounds.[1] Among the many methods available, enantioselective allylation of imines is one of the most straightforward and efficient methods to obtain homoallylic amines.[1,2] However, enantioselective imine allylation has its drawbacks as the allylation of enolizable imines can be complicated with side reactions (Figure 1).[2b,c] Furthermore, the allylations were mostly γ-regioselective, affording branched homoallylic amines. As far as we know, there has been no report on α-regioselective imine allylation with good enantioselectivity.

Based on our recent work on 2-oxonia-[3,3]-sigmatropic rearrangement in the synthesis of linear homoallylic alcohols,[3] we envisage that the 2-aza-[3,3]-sigmatropic rearrangement of the corresponding nitrones, easily obtained from hydroxylamines, will afford the synthetically versatile linear homoallylic hydroxylamines/nitrones.[4] Herein, we report a synthesis of linear homoallylic nitrones

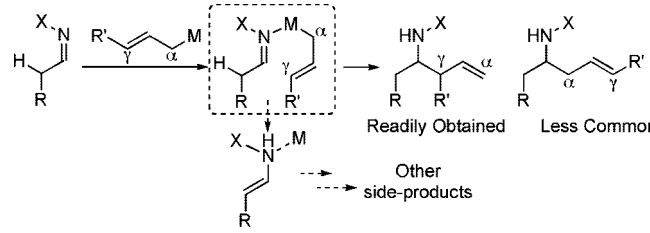


Figure 1. Challenges in imines allylation.

(1) For reviews, see: (a) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (b) Hall, D. G.; Kennedy, J. W. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 4732. (c) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed* **2008**, *47*, 258.

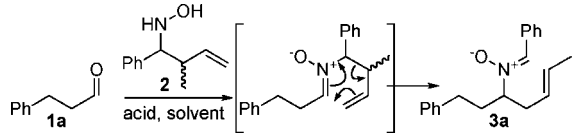
(2) (a) Kleinman, E. F.; Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: New York, 1991; Vol. 2, p 975. (b) Ding, H.; Friestad, G. K. *Synthesis* **2005**, 2815. (c) Merino, P.; Tejero, T.; Delso, J. I.; Mannucci, V. *Curr. Org. Synth.* **2005**, *2*, 479.

(3) (a) Loh, T. P.; Tan, K. T.; Hu, Q. Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 2921. (b) Loh, T. P.; Tan, K. T.; Yang, J. Y.; Xiang, C. L. *Tetrahedron Lett.* **2001**, *42*, 8701. (c) Cheng, H. S.; Loh, T. P. *J. Am. Chem. Soc.* **2003**, *42*, 4990. (d) Nokami, J.; Yoshizane, K.; Matsuura, H.; Sumida, S. *J. Am. Chem. Soc.* **1998**, *120*, 6609. (d) Sumida, S.; Ohga, M.; Mitani, J.; Nokami, J. *J. Am. Chem. Soc.* **2000**, *122*, 1310. (e) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815. (f) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919. (g) Marumoto, S.; Jaber, J. J.; Vitale, J. P.; Rychnovsky, S. D. *Org. Lett.* **2002**, *4*, 3919.

10.1021/ol800925v CCC: $40.75
Published on Web 06/07/2008

using the branched homoallylic nitrone generated in situ from aldehyde and branched homoallylic hydroxylamines. Initial studies were done by subjecting the readily available branched homoallylic hydroxylamine **2**[5] with hydrocinnamaldehyde **1a** in the presence of Lewis acids or Brønsted acids under various reaction conditions. The results are summarized in Table 1.

Table 1. Rearrangement of Branched Homoallylic Nitrones Generated in Situ To Form Linear Homoallylic Nitrones



entry	**2**/equiv (syn/anti)	acid/0.2 equiv	solvent	time/h	yield[a]/%
1	3.0 (50:50)	$In(OTf)_3$[b]	CH_2Cl_2	4	70
2	3.0 (50:50)	CSA	CH_2Cl_2	5	85
3[c]	**1.1 (50:50)**	**CSA**	**CH_2Cl_2**	**5**	**81**
4	1.1 (50:50)	CSA	MeOH	72	5
5	1.1 (50:50)	CSA	THF	12	54
6[d]	1.1 (**100:0**)	CSA	*i*PrOH	7	80
7[e]	1.1 (**0:100**)	CSA	*i*PrOH	4	82
8[f]	1.1 (50:50)	-	*i*PrOH	120	0

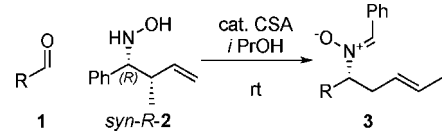
[a] Isolated yield. [b] 0.1 equiv of $In(OTf)_3$ was used. [c] ^1H NMR monitoring showed that the rate of reaction of the anti isomer is faster than that of the syn isomer. [d] Syn isomer of **2** was used. [e] Anti isomer of **2** was used. [f] No acid was added.

This reaction worked well in the presence of Lewis acid or Brønsted acid catalysts to afford the desired product in moderate to good yields (Table 1). The reaction was found to proceed smoothly under both protic and aprotic solvents (Table 1, entries 2−7). To our surprise, regardless of the stereo geometry of the starting material **2**, all the products obtained were exclusively the *E*-isomers. This result is in contrast to the reaction involving the 2-oxonia-[3,3]-sigmatropic rearrangement.[3]

With this result in hand, we proceeded to investigate the asymmetric version of this new hydroxylaminoallylation reaction. A readily available optically pure starting material, *syn-R*-**2**,[6] was subjected to the optimized reaction conditions.

In all cases, the desired linear homoallylic nitrones were obtained in good yields with excellent enantioselectivities. Even with enolizable aldehydes, the products were obtained in good yields with excellent enantioselectivities of up to 99% (Table 2, entries 1−2 and 5−7). The rate of reaction was affected by the steric bulkiness of the aldehydes. While the reactions with primary and secondary aldehydes proceeded smoothly at room temperature, the reactions involving tertiary and aromatic aldehydes were very slow at room temperature and heating was necessary to drive the reactions to completion.

Table 2. Asymmetric Synthesis of Nitrones



Entry	R-	Product	Time /h	Yield[a,b] /%	ee /%
1	Ph	**3a**	7	80	99
2		**3b**	24	95	98
3		**3c**	12 (Δ48)[c]	86	94
4	Ph-	**3d**	12 (Δ72)[d]	88	92
5	BnO	**3e**	12	72	97
6	BnO	**3f**	12	74	98
7	BnO	**3g**	36	70	97
8[e]	Ph	**3a**[f] *(S-isomer)*	4	82	99

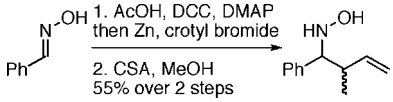
[a] Isolated yield. [b] Absolute stereochemistry was confirmed by matching chiral HPLC data with known product. [c] Heated at 50 °C for 48 h after 12 h at rt. [d] Heated at 50 °C for 72 h after 12 h at rt. [e] *anti-R*-**2** was used in place of *syn-R*-**2**. [f] *S*-Isomer was obtained.

Remarkably, the only product obtained, **3′′**, possessed *E*-geometry, which stereochemically corresponded to the minor product, **3o′′**, in the 2-oxonia-[3,3]-sigmatropic rearrangement,[3] while **3′** was not observed although it stereochemically corresponded to the major product in the 2-oxonia-[3,3]-sigmatropic rearrangement (Figure 2). The *E*-geometry of one of the products, **3d**, was confirmed by X-ray crystallography. The absolute stereochemistry of this compound was determined by comparing HPLC retention times.[7]

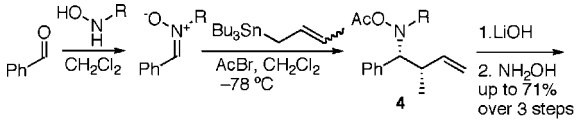
Furthermore, when the [3,3]-sigmatropic rearrangement of optically active homoallylic nitrone **N1** was studied, it was found that the enantiomeric excess of product **N2** dropped significantly. This observation differed from a previous report on 2-aza-[3,3]-sigmatropic rearrangement,[4e] where the enantiomeric excess was maintained.[4d]

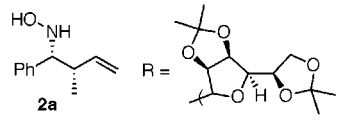
(4) (a) Horowitz, R. M.; Geissman, T. A. *J. Am. Chem. Soc.* **1950**, *72*, 1518. For a review, see: (b) Przheval'skii, N. M.; Grandberg, I. I. *Usp. Khim.* **1987**, *56*, 814. (c) Overman, L. E. *Acc. Chem. Res.* **1992**, *25*, 352. (d) Wuts, P. G. M.; Jung, Y. W. *J. Org. Chem.* **1988**, *53*, 1957. (e) Kobayashi, S. M.; Mori, C.; Kobayashi, S. *J. Am. Chem. Soc.* **2006**, *128*, 11038.

(5) Synthesized from benzaldehyde oxime. See the Supporting Information for details.



(6) Readily obtained in gram-scale from nitrone. See the Supporting Information for details.





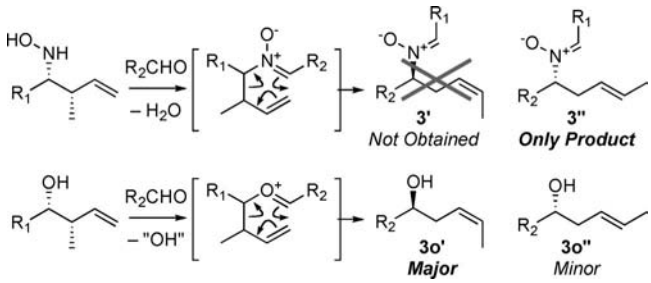
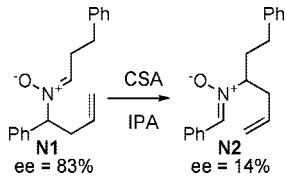
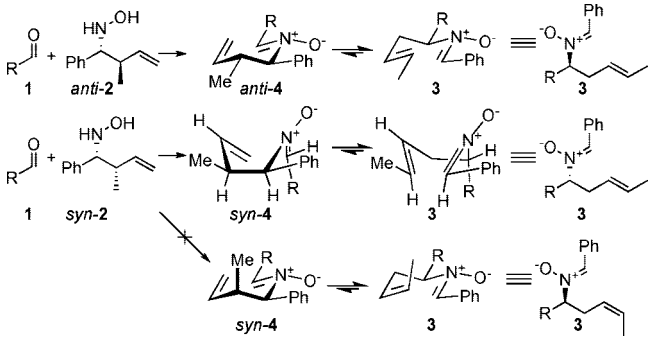


Figure 2. 2-Aza- and 2-oxonia-[3,3]-sigmatropic rearrangements.[3]



Hence, the following transition states are proposed to account for the outcome in stereochemistry and exclusive *E* selectivity (Scheme 1), based on the fact that oximes readily

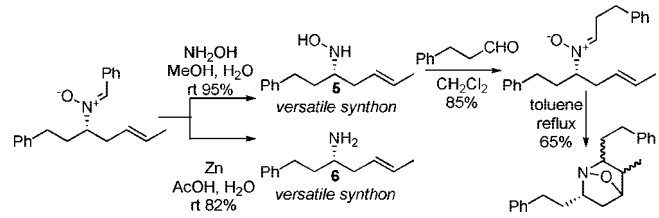
Scheme 1. Proposed Mechanism



go through both chair and boat conformers in their Zimmermann−Taxler transition states.[8]

While the [3,3]-sigmatropic rearrangement of nitrone *anti*-**4** clearly goes through the most stable chair transition state, the rearrangement of *syn*-**4** has to proceed via the boat transition state, thus avoiding the unfavorable 1,3-diaxial interaction, to afford the *E*-isomer. The stereochemistry of the methyl group is crucial in determining the conformer of the transition states and hence directed the stereochemical outcome of this [3,3]-sigmatropic rearrangement.

Scheme 2. Synthetic Applications of Nitrone



We have also demonstrated the versatility of the homoallylic nitrone **3a** (Scheme 2). It can be readily converted into linear homoallylic amine **6**, which is widely used in synthesis.[2] More importantly, **3a** can be readily converted into homoallylic hydroxylamine **5**, a valuable synthon which can easily be transformed into a diverse array of nitrones for various 1,3 dipolar reactions.[9]

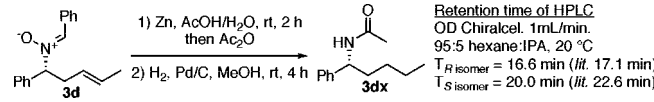
In conclusion, a direct access to linear homoallylic nitrones has been realized under very mild reaction conditions affording good yields and excellent enantioselectivities. Further application of this methodology in both divergent synthesis and the synthesis of alkaloids is in progress.

Acknowledgment. We thank Nanyang Technological University for the generous financial support and thank the Singapore Millennium Foundation Ltd. for its scholarship support of H.-S.C.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

OL800925V

(7) **3dx** was converted from **3d**. The HPLC retention time matches well with the literature value. Aggarwal, V. K.; Guang, Y. F.; Schmidt, A. T. *J. Am. Chem. Soc.* **2005**, *127*, 1642. See the Supporting Information for details.



(8) Hoffmann, R. W.; Endesfelder, A. *Liebigs Ann. Chem.* **1987**, 215.

(9) Two isomers were isolated with stereochemistry undetermined. For examples of intramolecular 1,3-dipolar cycloaddition, see: (a) Looper, R. E.; Williams, R. M. *Angew. Chem., Int. Ed.* **2004**, *43*, 2930. (b) Budzinska, A.; Wojcienchi, S. *Tetrahedron* **2001**, *57*, 2021. (c) Lumma, W. C., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 2920.